International Journal of Pharma and Bio Sciences
ISSN 0975 - 6299

AICTE SPONSORED NATIONAL SEMINAR

ON

NEW HORIZONS IN DRUG DISCOVERY AND DEVELOPMENT

17TH -18TH SEP, 2011
VENUE: CONVENTION CENTRE
HALL-1, JAMIA HAMDARD

ORGANIZED BY

Department of Pharmaceutical Chemistry

Faculty of Pharmacy, Jamia Hamdard
Hamdard Nagar, New Delhi-110062
www.jamiahamdard.edu

Proceedings of AICTE Sponsored National Seminar on
New Horzons in Drug Discovery And Development - September 17th and 18th , 2011

International Journal of Pharma and Bio Sciences
ISSN 0975 - 6299

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International Journal of Pharma and Bio Sciences
ISSN 0975 - 6299

PROCEEDING -1

DRUG UTILIZATION PATTERN OF ANTIBIOTICS USED IN LOWER RESPIRATORY TRACT INFECTIONS

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INTRODUCTION: Lower respiratory tract infections (LRTIs) are the most prevalent, the most frequently fatal and cost-intensive infectious diseases worldwide. They include acute bronchitis, bronchiolitis, pneumonia and tracheitis. Antibiotics are commonly prescribed for RTIs in adults and children in primary care. Prescribing patterns for antibiotics for RTIs vary widely among general practices. Despite many years of clinical use of antibiotics, little is known about how these drugs should be used optimally in the clinic. A central and still largely unanswered question is how antibiotics should be administered clinically to minimize resistance development without compromising safety and efficacy. Therefore, studies reflecting drug utilization patterns are required, as they assess the appropriateness of drug therapy.

EXPERIMENTAL DESIGN: During the study period of 4 months, a total of 2100 patients (suffering from various diseases) visited the outpatient and inpatient department of Medicine, Majeedia Hospital. Out of these patients, only 110 patients (suffering from bronchitis and pneumonia infections) met the inclusion criteria and were included in the study.

RESULTS AND DISCUSSION: A gender distribution of the subjects indicated 67.27% of males and 32.72% of females. The distribution of patients in OPD and IPD was 86 (78.18%) and 24 (30.9%) respectively. It was observed that maximum number of patients (27.27%) was under the age group of 56-65 years. We observed that 54.54% patients taken antibiotic monotherapy and the remaining patients were on multiple therapy receiving 2, 3 or 4 drugs per prescription. The average number of antibiotic agent prescribed per patient per course was found to be 3.97. The number is much higher than other studies (Ain et al, 2010; Das et al, 2003). An average of 3.75 drugs per prescription indicates polypharmacy. Since it increases the risk of adverse effect, drug interaction, increases cost and reduce patient compliance; it is an area of concern requiring intervention.

The average number of drugs per prescription was 3.97. The most frequently prescribed antibacterials were β-lactams (45.53%) followed by quinolones (26.27%). The most commonly used agents in penicillins was amoxicillin with clavulanic acid (20.82%) followed by gemifloxacin (13.95%) and chloremphenicol (10.06%). The routes of administration of antibiotic were found to be oral (81.81%), parentral (9.09%) and topical (inhalation) (9.09%). All the antibacterial agents were prescribed by their brand names only. Such practice may be an evidence of vigorous promotional strategies by pharmaceutical companies. It may undermine some of the goals of essential drug concept. On the other hand, prescribing by generic name may reduce overall expenditure on drugs especially on newer antibiotics etc. The practice of prescribing drugs by brand name thus should be discouraged as use of generic is a cheaper alternative.

45.45% patients showed a good adherence with the prescribed treatment. A significant number of patients (82.64%) were found to be suffering from concomitant diseases. The most frequent co-morbid condition of the study population was found to be diabetes (25.45%), followed by hypertension (16.36%), coronary artery disease (11.81%), hypothyroidism (8.81%) and rheumatoid arthritis (3.63%). Further only 50 (45.45%) patients

had taken the drug properly. For studying patients compliance weekly diary cards where used. Cost of antibiotic could be one of the important factors for noncompliance in developing countries like India. Inadequate information about the disease, adverse effect of the drugs, use instructions and cautions are the other reasons of patients' non-compliance (Ryan, et al., 2003).

CONCLUSIONS: It appears that majority of LRTIs patients coming to the hospital are primarily due to bacterial infections, as they responded well with the use of antibacterials. Majority of the patients used regimen to the current guidelines. Prescribing drugs by generic names and not by brand names could decrease the cost of the treatments.

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PROCEEDING -2

FORMULATION DEVELOPMENT & CHARACTERIZATION OF PLGA BASED POLYMERIC MICROSPHERE ENCAPSULATING OFLOXACIN FOR THE TREATMENT OF PERIODONTAL DISEASE

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INTRODUCTION:

Periodontal disease is a term generalized to denote a group of inflammatory pathological condition of periodontal ligaments, alveolar bone and dental cementum resulting in massive degeneration of supporting tissue of teeth [1]. Bacterial infection is believed to be the root cause for initiation of the disease where bacteria produce degenerative by products and enzymes that lead to break down of extracellular matrix and cellular membranes of host tissues. Ofloxain is a fluoroquinolone antibiotic effective against anaerobes and gram positive microorganisms. Hydroxyapatite (HA) has been used in treatment of periodontitis due to structural similarity to bone and hence utilized as a bone substitute [2]. It is a biomaterial belonging to the class of calcium phosphates and available as blocks, granules and porous structures. HA is propsed to be an osteo integrator due to its bioactivity. PLGA or Poly (Lactic –Co-glycolic acid) are biocompatible and biodegrable polymers and microspheres based on PLGA extensively used in sustained drug delivery applications and also as cell carriers. Drug is encapsulated in PLGA polymer to prepared microsphere as a drug delivery system with prolonged antibiotic release for local action to treat periodontitis. The objective of the present study was to formulate a low dose drug delivery system which could be easily and conveniently placed in the periodontal pocket and maintained at a drug concentration above the minimum inhibitory concentration inside the periodontal pocket without causing any deleterious side effects. In the present study the effect of ofloxacin used an antibacterial drug encapsulated in PLGA microsphere using hydroxyapetitite (HA) into the periodontal pocket where it would deliver the drug for a sustained effect. The formulations were evaluated for particle size distribution, TEM, SEM, microbiological evaluation, *in vitro* release (Fig. 1) and *in vitro* biocompatibility studies using MTT assay.

EXPERMIENT AND METHODOLOGY:

Ofloxacin was obtained as a gift from Unicure. Poly (d,l-lactide-co-glycolide) (PLGA, 50:50, MW 40,000–75,000) (PLGA 50:50) was a humble gift from NII, Delhi, India. Hyaluronic acid was purchased from sigma Aldrich Chemical Inc. (Munich, Germany). All the other reagents used were of analytical reagent grade. The microspheres were synthesized by the single emulsion solvent evaporation method [4]. The drug was taken in a 25 ml volumetric flask to which sufficient amount of DCM was added to make up the final volume. The system was subjected to a brief sonication cycle to dissolve the drug. The drug solution was taken and a prefixed quantity of polymer added to it (as per formulation scheme) with continuous stirring until it dissolved completely. A preweighed quantity of HA was then added to drug- polymer solution and sonicated for one minute to form a uniform suspension. The resulting microspheres were centrifuged at 10000 rpm for 15 minutes. The supernatant was then washed off and the microspheres settled at the base were filtered out and washed many times with distilled water in order to remove even the traces of residual solvent. The microspheres were finally freeze-dried for a night so as to remove water completely and then stored at 4°C for further evaluation.

RESULTS AND DISCUSSION:

The optimized formulation loaded with drug exhibited better particle morphology having excellent microparticle showing a size range of 22.05 ± 5µm. The optimized formulation revealed spherical microspheres and smooth homogenous surface of PLGA with no porosity was clearly observed using SEM. Presence of some rough surface could be attributed to the presence of solid HA. The optimized formulation with an encapsulation efficiency of 61.28 % and particle size of 22.04 µm which was in high correlation with predicted values, hence the statistical model employed was valid and reliable. The *in vitro* drug release study revealed a sustained drug release up to 12 days. Average drug release of 49.83 µg/ day was way above the MIC values for antibacterial activity of ofloxacin. Biocompatibility studies using MTT assay was also marked for HA supplemented cultures, indicating that the presence of the antibiotic and HA, may have a beneficial effect in cell proliferation.

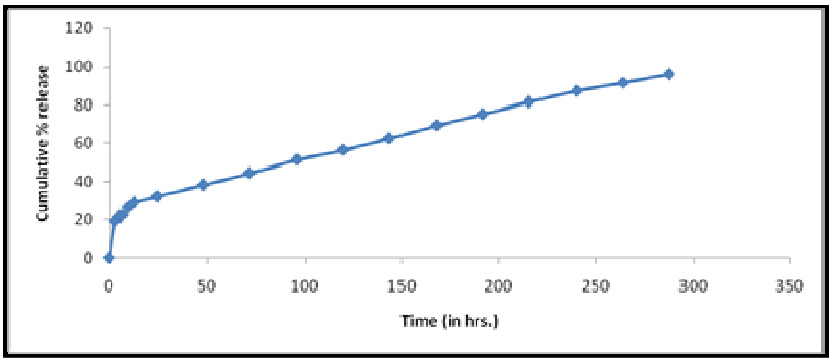

Figure:1
Cumulative percent drug release of optimized formulation

CONCLUSION:

It could be concluded that the present research work successfully attempted to develop an optimized ofloxacin, HA loaded microspheres of PLGA. From the evaluation reports it could be further concluded that it could suitably be employed for clinical effectiveness in patients suffering from periodontal infections. A local drug delivery system with a much smaller dose with minimum or no side effects would definitely act as a better alternative in comparison to conventional formulations, where large quantity of drugs are administered thus

leading to accentuated adverse drug affects. The purported system which is composite in nature used the available polymers not merely as platform of drug delivery but for their therapeutic effect. Therefore the proposed system would give a synergetic effect of having an antimicrobial activity as well as being a source for rectification of infrabony / osseous dental effects. The agent could be easily and conveniently placed in the periodontal pocket by a single administration and which is proposed to achieve and maintain therapeutic concentrations within the crevicular fluid throughout the duration of therapy.

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PROCEEDING -3

EFFECT OF *SOLANUM TORVUM* ON THE CONTRACTILE RESPONSE OF ISOLATED TISSUES PREPARATION IN FRUCTOSE FED RAT

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INTRODUCTION

Hypertension, glucose intolerance and dyslipidemia are well established risk factors for cardiovascular diseases. High fructose diet has been documented to increase dyslipidemia and blood pressure in experimental rats. Fructose feeding also activates the renin-angiotensin system (RAS), sympathetic nervous system and it can be affect the serotonergic system. We examined the effect of ethanolic extract of *Solanum torvum* (*S. torvum*) on isolated strip of ascending colon, Fundus and Vasdeferens in fructose (10%) fed rat.

EXPERIMENTAL METHODS

ANIMALS: Male albino rats (Wistar strain) weighing between 150-200 g, were obtained from Serum Institute, Pune. The experiments were carried out according to the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), New Delhi, India, and approved by the Institutional Animal Ethical Committee.

DRUG AND CHEMICALS: Angiotensin (Ang II), Serotonin (5-HT), Phenylepherine (PE) were purchased from Sigma, Mumbai. Fructose was obtained from Merck (India). Fructose (10%) were freshly prepared in distilled water.

METHODS: Mature fruits (*S. torvum*) were dried in shade and grounded. The powder obtained (1 kg) was defatted using pet ether (60–80 ◦C). The marc was macerated in ethanol for 3–4 days at room temperature. The filtrate was concentrated under reduced pressure to obtain 120 g of extract (12.0%, w/w). Rats received distilled water or fructose (10%, w/v) with or without *Solanum torvum* (100 or 300 mg/kg p.o.) for 6 weeks. After completion of the treatment schedule, rats from individual groups were sacrificed. Cumulative concentration response curve (CCRC) of Ang II (10 ng/ml), 5-HT (10 µg/ml) and PE (10 µg/ml) were performed using

ascending colon, Fundus and Vas deferens. The physiological salt solution had the following composition (mM) NaCl (118); KCl (4.7); CaCl2 (2.5); MgSO4 (1.2); NaHCO3 (25); KH2PO4 (1.2) and glucose (11). The physiological salt solution had a pH of 7.4

RESULTS AND DISCUSSION

It is well known that the magnitude of vascular responses to Ang-II and 5-HT was significantly ($p<0.05$) enhanced in high fructose fed rats. Increased Ang-II vascular responses in high fructose fed rats may be due to upregulation of Ang-II receptors as observed in hyperinsulinemia. Chronic administration of *S. torvum* extract (100, 300 mg/kg/day, p.o.) for 6 weeks in fructose rats significantly ($p<0.05$) shifted the CCRC of Ang-II and 5-HT to the right. This indicates inhibitory effect of *S. torvum* on Ang-II and 5-HT receptors. CCRC of Phenylephrine using isolated Vas deferens was significantly ($p<0.05$) rise in rats cotreated with *S. torvum* (100, 300 mg/kg/day, p.o.). *S. torvum* possess potent *in vitro* vasocontractile activity on Vas deferens that may result from activation of both α_1-adrenergic pathway and calcium influx.

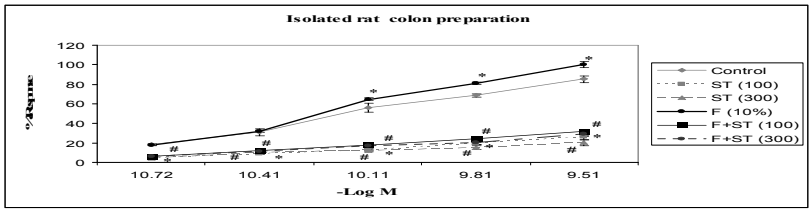

Figure 1:

Effect of S. torvum (100, 300 mg/kg, p.o., for 6 weeks) on CCRC of Ang-II on isolated rat ascending colon in fructose (10 %) fed rats

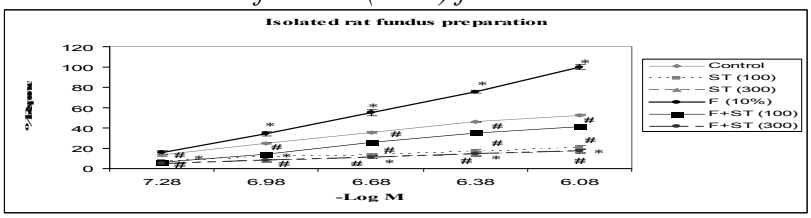

Figure 2:

Effect of S. torvum (100, 300 mg/kg, p.o., for 6 weeks) on CCRC of 5-HT on isolated stomoch fundus strip in fructose (10 %) fed rats.

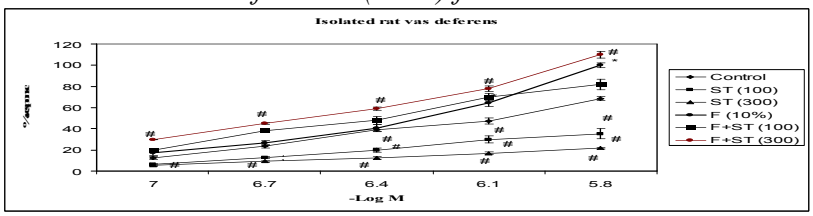

Figure3

Effect of *S. torvum* (100, 300 mg/kg, p.o., for 6 weeks) on CCRC of PE on isolated Vas deferens in fructose (10 %) fed rats.

SUMMARY

Chronic administration of *S. torvum* could block the Ang-II and 5-HT receptor and it also activate α_1-adrenergic pathway.

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International Journal of Pharma and Bio Sciences
ISSN 0975 - 6299

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PROCEEDING -4

Identification of decontamination product of Mechlorethamine by GC-MS

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INTRODUCTION

Mechlorethamine also known as chlormethine, mustine and HN2, is an antineoplastic alkylating agent sold under the brand name Mustargen. It is used for the treatment of Hodgkin disease, lymphosarcoma, chronic myelocytic or chronic lymphocytic leukemia, mycosis fungoides, bronchogenic carcinoma, and polycythemia vera[1]. Chemotherapy agents, such as mechlorethamine, pose additional safety risks both for patients and for healthcare workers handling these agents[2]. In case of accidental exposure immediate removal is required and conversion of HN2 into non toxic form (decontamination) is the best method. N,N'-dichloro-bis[2,4,6-trichlorophenyl]urea) (known as CC2) was chosen for the oxidative decontamination of HN2 and a suspension of which was formulated.

EXPERIMENTAL METHODS

- **SAMPLE PREPARATION FOR DECONTAMINATION STUDIES**

To 20µl of HN2, was added to 500mg of formulation and vortexed for 1 min in a test tube. 3ml of dichloromethane was added to the test tube and vortexed for 3 min and centrifuged at 1500 rpm for 5 min. 1µl aliquot of the dichloromethane layer was injected in GC-MS.

- **IDENTIFICATION OF DECONTAMINATION PRODUCT**

The decontaminated products were identified by GC-MS using a capillary column with a polar stationary phase. A HP 6890 gas chromatograph equipped with a split/splitless injector and coupled to a HP 5973-quadrupole mass spectral detector was used throughout the analysis. The analytical column used was a 30 m × 0.32 mm ID and 0.25 µm film thickness with BP-5 stationary phase (SGE, Australia). The chromatograph was programmed from an initial temperature of 50°C, held at isothermal for 2 min and then increased at a rate of 10°C min^{-1} to a final temperature of 280°C and kept isothermal for 5 min (total run time 30 min). The temperature of the injector, MS interface, MS source and MS quadrupole were kept at 250°C, 280°C, 230°C and 150°C, respectively. Helium was used as the carrier gas at a flow rate of 1.2 mL min^{-1}. The mass spectrometer was operated in the electron impact ionisation mode at 70 eV.

RESULTS AND DISCUSSION

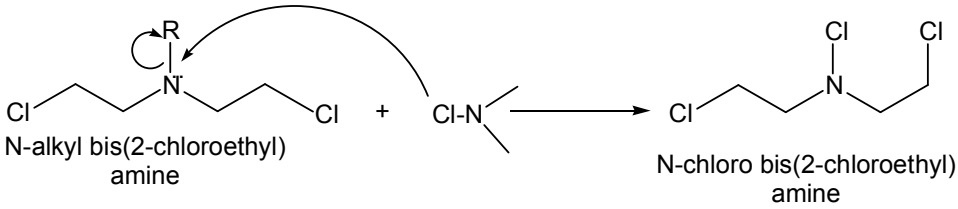
Gas chromatography-mass spectrometry (GC-MS) can be used to identify unknown compounds based on their retention parameters, and interpretation of mass spectral fragmentation patterns. The combination of GC and MS is capable of detecting a wide range of toxic agents, providing high selectivity and sensitivity, as well as providing structural information about these compounds[3].

The GC-MS analysis was performed for the standard HN2 solutions before the decontamination studies. The HN2 gave GC peak at 3.06 min. The mass spectra of HN2 was recorded. Mass (EI): m/z: M^+(155), 157 $(155+2)^+$, 106$(M-49)^+$, 108$(120+2)^+$, 78$(M-77)^+$, 80$(78+2)^+$, 63$(M-92)^+$, 65$(63+2)^+$

It was observed that after decontamination of HN2 with CC2, dichloromethane layer did not yield any peak corresponding to HN2 showing the reaction of CC2 and HN2 is complete and immediate. N-chloro bis(2-

chloroethyl) amine was identified as the decontamination product of HN2. Mass (EI): m/z: M^+(175), 126(M-49)$^+$, 92(M-84)$^+$, 63(M-112)$^+$.

The reaction can be summerised as follows:



SUMMARY

It can be concluded that HN2 can be decontaminated effectively and immediately into non toxic product. Hence CC2- formulation can be used by the health care professionals before and after handling HN2 dosage forms.

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PROCEEDING -5

Microbial Transformation of Eugenol to Vanillin

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INTRODUCTION

Lignin-related phenylpropanoides such as eugenol and isoeugenol, which is the main component of clove essential oil, serve as a potential substrate for the production of valuable aromatic compounds (Rao and Ravishankar 1999; and Overhage *et al;* 1999, 2003).). In the present study, to find microorganisms showing high vanillin-producing activity, we carried out an extensive screening of eugenol-degrading microorganisms and attempted the conversion of eugenol to vanillin using resting cells of *Bacillus species* strain BR, a novel eugenol-degrading bacterium.

MATERIALS AND METHODS

Enrichment culture, screening and biotransformation of bacterial strain

For the isolation of eugenol-degrading microorganisms, a conventional enrichment culture was carried out at 37 °C. Strain BR used in this study was isolated from soil of *Ficus* field. A pure culture was obtained by streak plating a sample of the enrichment culture broth into nutrient agar medium poured in glass petri plates. Cells were grown in a 500-mL flask containing 50 mL of biotransformation (BT) medium (0.3% beef extract, 0.5% peptone, 0.5% NaCl, pH 7.0) supplemented with 0.2% isoeugenol was used at 30 °C and 180 rpm for 72 h. Cells, which were found positive for biotransformation of eugenol to vanillin in initial screening, were grown on BT medium at 30 °C and 180 rpm for 24 h, and eugenol was added up to 0.2% concentration. Growth was monitored turbidometrically at 660 nm.

RESULTS

Using the soil isolates and growth kinetic study of bacteria performed in our laboratory, vanillin-producing activity was examined by the resting cells reaction. The maximum yield of vanillin appeared at 48 h when 0.32

mg/l of vanillin was detected in the culture. After transformation, five prominent products were detected in the extracts of culture by GC (retention times were 10.251, 12.392, 12.936, 13.721 and 14.658 min). Metabolite with retention time of 12.392, which was identified as vanillin. The resting cells of *Bacillus species* acted on eugenol to produce vanillin as well as on DMSO for increasing the yield of vanillin. The conversion was reflected by the shift in UV absorption pattern**.** The degradation of eugenol and the accumulation of metabolites in the culture supernatant were quantified by HPLC.

DISCUSSION

In previous studies on the bioconversion of eugenol, the cell-free extract of *Bacillus species* transformed isoeugenol into vanillin with a molar yield of 14% by a 48 h reaction, the product concentration being 0.9 g/l of the reaction mixture (Shimoni et al. 2000). In the present study, we have attempted to optimize the culture and reaction conditions to enhance the productivity of vanillin from eugenol using *Bacillus species* strain BR. The addition of 0.2% (v/v) DMSO enhanced its solubility, resulting in higher vanillin productivity.

CONCLUSIONS

The resting cells of *Bacillus species* attained 0.32 mg/l vanillin (0.002 mM) from 0.0128 mM isoeugenol with a molar conversion yield of 15.6% after a 48 h incubation in the presence of 0.2% (v/v) DMSO.

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PROCEEDING -6

Synthesis of some new 4-Thiazolidinone derivatives as anticonvulsant agents

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INTRODUCTION

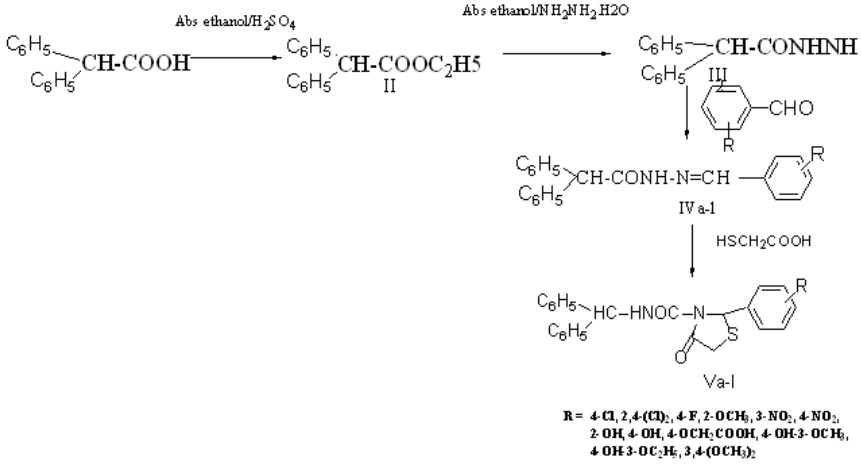
A common chronic neurological disorder i.e. epilepsy is characterized by recurrent unprovoked seizures. Despite the development of several new anticonvulsants the treatment of epilepsy remains still inadequate, and the patients suffer from a lot of specific problems like neurotoxicity, depression and other CNS related diseases. Thus, it is essential to search for newer chemical moities for the treatment of epilepsy.

Derivatives of 4-thiazolidinone have attracted because of their varied biological activity such as antimicrobial, anticancer, antitubercular, anti-inflammatory, analgesic, neurotoxity and anticonvulsant activities. In the present paper, we report the synthesis, anticonvulsant and neurotoxicity study of a series of *N* 1-[2-(substituted phenyl)-4-oxo-1, 3-thiazolan-3-yl]-2, 2-diphenylacetamides (Va-l).

International Journal of Pharma and Bio Sciences
ISSN 0975 - 6299

EXPERIMENTAL METHODS

Some new N 1-[2-(substituted phenyl)-4-oxo-1, 3-thiazolan-3-yl]-2, 2-diphenylacetamides (Va-l) derivatives and hydrazones (IVa-l) were synthesized by treating diphenyl acetic acid with abs. ethanol in presence of conc. H_2SO_4 to give Diphenyl ester (I), which was treated with hydrazine hydrate to give corresponding hydrazide (II). The hydrazide was then treated with different arylaldehydes to give the corresponding hydrazones (IVa-l) and then treated with thioglycolic acid to obtained novel N 1-[2-(substituted phenyl)-4-oxo-1, 3-thiazolan-3-yl]-2, 2-diphenylacetamides (Va-l). All the final compounds were structurally elucidated on the basis of IR, ^{1}H-NMR, MS data and elemental analysis.The final compounds were evaluated for their anticonvulsant activity and neurotoxicity by maximal electroshock seizure (MES) method and rotarod method respectively.



RESULTS AND DISCUSSION

All the tested compounds were dissolved in propylene glycol -400 and administered, each in albino mice (Swiss strain) .The compounds IVb, IVc, IVg, IVj, IVk, Ve and Vf exhibited most potent anti-MES activity. The compounds IVc, IVk, Vb , Vd, and Vg successfully passed the rotorod test without any sign of neurological deficit whereas the compounds IVa, IVd, IVf, IVg, IVh, IVl, Vc, Ve, Vf and Vh exhibited neurological deficit at dose of 300 mg/kg i.p. The compounds IVb, IVg, IVk, Va, Vf and Vr were found to be more lipophilic having potent anticonvulsant activity. The other compounds IVd, IVh, IVi, IVj, IVl, Vb and Vc were also lipophilic having same potency. Thecompounds IVa, IVc, IVe, IVf, Vd, Ve and Vg are less lipophilic and are less active in MES test.

SUMMARY

It can be revealed that electron withdrawal group in position 2 and 4[disubstituted phenyl-4-oxo-1,3-thiazolan-3-yl]-2,2-diphenyl acetamides was essential for the activity. Thus a number of novel N 1-[2-(substituted phenyl)-4-oxo-1,3-thiazolan-3-yl]-2,2-diphenyl acetamides derivatives exhibited anticonvulsant Screening and Neurotoxicity Screening by using MES test and Rotarod respectivily. Some compounds like IVb, IVg, IVk, , IVm, Vf and Vh showed more lipophilic character and were more active.The compounds IVa, IVd, IVh, IVi, IVj, IVl, Vb, Vc and Vd were also lipophilic but were less active in MES test.

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PROCEEDING -7

SYNTHESES AND EVALUATION OF ANTIDEPRESSANT AND ANXIOLYTIC ACTIVITIES OF SOME NEW ISOXAZOLE DERIVATIVES CONTAINING QUINOXALINE MOIETY

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INTRODUCTION

According to various estimates, over two-third of patients suffering from depression, whether in clinical or in the general population, have prominent anxiety symptoms, and a third of these subjects may meet the diagnostic criteria for various anxiety disorders. Benzodiazepines are the most widely used anxiolytics. However, these compounds often produce undesirable side effects, including sedation, physical dependence, amnesia and ethanol potentiation. For this reason there is need for non–benzodiazepine compounds with potential anxiolytic activity. This motivated us to synthesize new compounds in search of antidepressants and anxiolytics that are devoid of or exhibit markedly reduced side effects. Isoxazoles are reported to have antidepressant and antianxiety activity. Isocarboxazide is an isoxazole nucleus containing drug which is used as an antidepressant. Similarly quinoxalines are also reported to have various biological activities including antimicrobial, anti-cancer, antiviral, anti-inflammatory and antidepressant. Based on these reportings we decided to synthesize some new compounds bearing isoxazole and quinoxaline nucleus with aim to obtain better antidepressants and anxiolytics.

EXPERIMENTAL

Melting points were determined by the open capillary tubes and are uncorrected. Purity of the compounds was checked by TLC and spots were located under iodine vapors. IR spectra were recorded as KBr (pellet) on Bio Rad FT-IR spectrophotometer. 1H-NMR spectra were recorded on Bruker DPX 300 MHz spectrophotometer using TMS as internal standard. The mass spectra were recorded on JEOL SX102/DA-6000 mass spectrometer.

GENERAL PROCEDURE FOR THE SYNTHESIS OF COMPOUNDS (1-3A-J)

Refluxing of o-phenylenediamine and pyruvic acid in absolute ethanol for 3 hr gave 3-methylquinoxalin-2(1*H*)-one **(1).** Compound **(1)** on reacting with appropriate aldehyde in presence of piperidine gave intermediates 3-[2-(x-phenyl)ethenyl]quinoxalin-2(1*H*)-one **(2a-j)**. Reaction of 3-amino-5-methyl isoxazole with **(2a-j)** afforded 5-methyl-*N*-[3-{2-(x-phenyl)-ethenyl}quinoxalin-2(1*H*)-ylidene]-1,2-oxazol-3-amine derivatives **(3a-j)**.

RESULTS AND DISCUSSION

The structures of all the new compounds have been established on the basis of their IR, ^{1}HNMR and mass spectra. The IR spectrum of compound **(3a)** showed characteristic absorption peak at 3379 cm^{-1} (NH), 1636 cm^{-1} (C=N), 3025 cm^{-1} (C-H str., Ar-H), 1362 cm^{-1} (C-O-N). The structure of the compound was further confirmed by its ^{1}H NMR spectrum, which showed a multiplet at δ 7.98-8.05 for (9H, CH) of aromatic ring. A singlet at δ 8.75 for (1H, NH), a doublet at δ 7.42 for (1H, =CH-Ar), a doublet at δ 6.88 for (1H, -CH=C) were obtained. The mass spectrum of compound **(3a)** showed molecular ion peak M+ at m/z 315 corresponding to molecular formula $C_{19}H_{15}N_4O$.

All the final compounds **(3a-j)** were evaluated for antidepressant activity (forced swimming method) and anxiolytic activity (elevated plus-maze method) using clomipramine and diazepam as standard drugs respectively. Compounds 3a, 3c, 3g, 3h, 3i and 3j showed significant antidepressant activity. Similarly compounds 3b, 3d, 3e and 3f showed moderate to significant anxiolytic activity.

CONCLUSION

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O-phenylenediamine was used as starting material to synthesize designed compounds 5-methyl-*N*-[3-{2-(x-phenyl)-ethenyl}quinoxalin-2(1*H*)-ylidene]-1,2-oxazol-3-amines **(3a-j)**. After establishing their structures, these compounds were screened for their antianxiety activity by elevated plus-maze method and antidepressant activity by forced swimming method. Diazepam and clomipramine were used as standard drugs respectively. Compounds 3a, 3c, 3g, 3h, 3i and 3j showed significant antidepressant activity. Similarly compounds 3b, 3d, 3e and 3f showed moderate to significant anxiolytic activity.

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PROCEEDING -8

Solid Self Nanoemulsifying Formulation of Glimepiride- In vivo Evaluation

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INTRODUCTION

Self nanoemulsifying formulations (SNEF) are isotropic mixtures of drug, oil/lipid, surfactant, and/or cosurfactant, which form fine emulsion, ranging in size from approximately 100nm to less than 50nm, on dilution with physiological fluid. These formulations have great potential to improve the absorption and hence bioavailability of BCS class II drugs in which absorption is limited by their dissolution step. The aim of the current study was to evaluate the in vivo efficacy of the formulated SSNEF for the oral delivery of glimepiride as compared to the pure drug.

EXPERIMENTAL METHODS

- **FORMULATION OF SOLID SELF NANOEMULSIFYING FORMULATIONS OF GLIMEPIRIDE:**

The solubility of the drug in different oils, surfactants and cosurfactants was determined. Further, construction of Pseudoternary phase diagrams and 3-factor Box-Behnken Design was done for the preparation and optimization of the formulations. The prepared formulations were further solidified by adding crospovidone XL as adsorbent carrier.

- **IN VIVO EVALUATION OF THE OPTIMISED SSNEF:**

In order to study the relative bioavailability of optimized SSNEF and pure drug *in vivo,* albino wistar rats were used as model animal. Animals were kept in standard laboratory conditions maintained at temperature 25 °C ± 2 and relative humidity 55 ± 5%. with free access to standard diet and water. The dose for rat was calculated on the basis of body weight of the animal. In the case of SSNEF, emulsifying granules corresponding to 1.33 mg glimepiride were weighed and separately dispersed in 100 ml of double distilled water. For the administration of pure drug (PD), a suspension of 1.33 mg drug in 0.5% CMC solution was prepared. The formulations were given orally by feeding sonde. The rats were anaesthetized using diethyl ether and blood samples (0.5 ml) were withdrawn from the tail vein of the rat in microcentrifuge tube which was first rinsed with EDTA. The microcentrifuge tubes were vortexed for 5 min and then centrifuged at 2000 rpm for 20 min. Plasma was separated and stored at -20°C until further drug analysis was carried out. The plasma samples were treated and analysed for drug content by LC-MS/MS system. Pharmacokinetics parameters

such as AUC, C_{max}, t_{max} and $t_{1/2}$ for each group were determined by using pharmacokinetic software and the values were expressed as mean ± SD.

RESULTS AND DISCUSSION

Depending on the results of the solubility studies labrasol, tween 20 and tween 40 were selected as the oil phase, surfactant and cosurfactant respectively. The optimized solid self nanoemulsifying formulation contained 2% w/w Labrasol and 40% w/w Tween 20. From the results of the in vivo study conducted using the optimized SSNEF, it was concluded that the $AUC_{0\rightarrow\infty}$ of SSNEF(483.27ng/ml/h) was nearly 1.4 folds higher as compared to orally administered pure drug (324.37 ng/ml/h). After oral administration of SSNEF the plasma levels of glimepiride reached a peak of 145.09 ng/ml at 1 h, while after oral administration of pure drug, it reached a peak of 100.6 ng/ml at 2 h. SSNEF showed a comparatively shorter T_{max} as compared to pure drug.

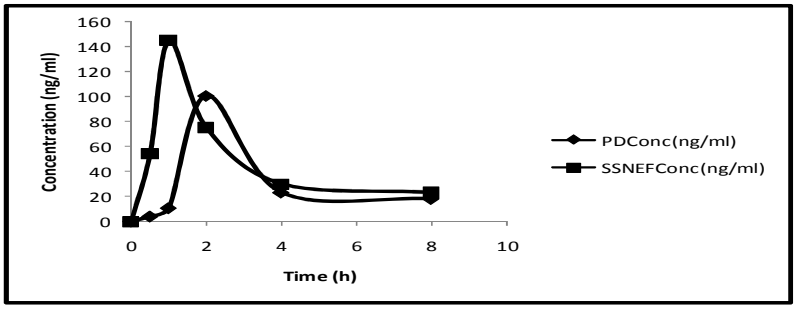

Fig. 1: Plasma concentration profile of glimepride

SUMMARY

It was concluded that the SSNEF resulted in increase in AUC0—t , AUC0--∞ , AUMC0—t , AUMC0--∞ and Cmax as compared to pure drug.

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PROCEEDING -9

"Synthesis of a series of fluoro chloro Benzimidazolo substituted thiazolidinone derivatives for better Anti-microbial activity"

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INTRODUCTION

Heterocycles bearing nitrogen, sulphur and thiazole moieties constitute the core structure of a number of biologically interesting compounds, Benzimidazolo substituted thiazolidinone derivatives are structural subunits of several biologically compounds, these are known to possess various pharmacological activities such as anti-bacterial, anti-fungal, anti-inflammatory and anti-tumour activities .

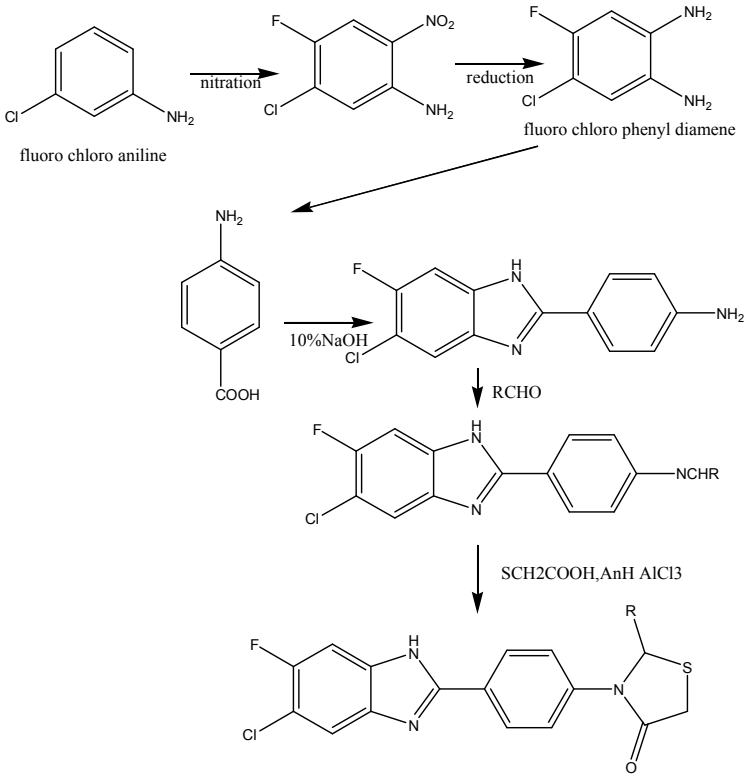
Further the Benzimidazolo substituted thiazolidinone derivatives have been reported for other anti-microbial activities .In view of the above and in continuation of search we have prepared several other derivatives by reacting fluoro chloro anilines followed by nitration and reduction forming fluoro chloro phenyl diamene

forming 4-amino benzoic acid ,at this step adding different substituted aldehydes will give the compounds which will further analyzed for yield and biological activity.

OBJECTIVE OF THE WORK

1. To carry out literature review and survey of various Benzimidazolo substituted thiazolidinone derivatives .
2. To synthesize some novel fluoro chloro Benzimidazolo-thiazolidinone class of derivatives.
3. To characterize the synthesized compounds by IR,NMR,and MASS spectroscopy.
4. To evaluate these synthesized derivatives for their biological activity.

METHODOLOGY



RESULT AND DISCUSSION

We have synthesize a series of 12 derivatives of fluoro chloro benzimidazolo substituted thiazolidinones with different aldehydes .Benzimidazole with aldehyde than reacted with the thioglycolic acid in presence of aluminium chloride to prepare fluoro chloro benzimidazoles that have been reported as anti-microbial agents .Derivatives are confirmed by the TLC, Melting point, IR, NMR, Mass spectroscopy.

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ISSN 0975 - 6299

PROCEEDING -10

Design and synthesis some newer benzothiazole derivatives as anticonvulsant agents

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INTRODUCTION

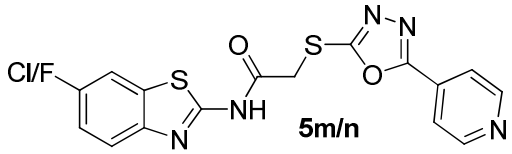
Heterocycles are ubiquitous among pharmaceutical compounds. Benzothiazole moiety is an important class of N and S containing heterocycle, widely used as key building blocks for pharmaceutical agents. It exhibits a wide spectrum of pharmacophore as it acts as bactericidal, fungicidal, analgesic, anticonvulsant and anti-tumor agents [1]. Similarly, oxadiazoles have also been reported to possess anticonvulsant activity [2]. Therefore the present study aims at design and synthesis of benzothiazole derivatives having oxadiazole moiety.

EXPERIMENTAL METHODS

General procedure for the synthesis of N-(6-substituted-1,3-benzothiazol-2-yl)-2-{[5-(aryl)-1,3,4-oxadiazol-2-yl]sulfanyl} acetamide: Equimolar quantity of 5-(aryl)-1,3,4-oxadiazole-2-thiol, sodium carbonate and 3-chloro-N-(substituted-1,3-benzothiazol-2-yl)acetamide was stirred in presence of DMF. After completing the reaction the mixture was poured in ice cold water, solid thus formed was filtered washed with water. The purity of the compound is checked by TLC using ethyl acetate as mobile phase. *N-(6-fluro-1,3-benzothiazol-2-yl)-2-{[5-(4-chlorophenyl)- 1,3,4-oxadiazol-2-yl]sulfanyl}acetamide (5a)*: IR (KBr) υ max, cm-1: 1677 (amide C=O), 1562 (C=N), 1294 (C-O-C). 1H NMR (400MHz, DMSO- d6) : δ 4.32 (s, 2H, SCH2), 7.10-7.92 (m, 7H, ArH), 12.67 (s, 1H, CONH).

RESULTS AND DISCUSSION

The synthesized compounds were evaluated for their anticonvulsant activity using MES and ScPTZ model [3]. In MES test at 0.5 h time period after drug administration, compounds that showed 100% protection at 30 mg/kg dose of the tested mice were 5m, 5n and 5o, whereas after 4 h compound 5a was 100 % effective. Compound that exhibited MES activity at both the 0.5 and 4 h time periods was 5m. All of the compounds inordinately exhibited anticonvulsant activity in both the MES and the sc-PTZ screenings. As a result of MES screening, compounds 5a, 5b, 5c, 5d, 5m, 5n, 5o and 5p were further subjected to Sc-PTZ screening in mice at 100 mg/kg dose. Compound 5n showed 100% protection after 0.5 h in Sc-PTZ test whereas compound 5m was 75% protective at both 0.5 and 4 h. In the CNS depressant studies, compounds 5a and 5m showed no increase in immobility time during Porsolt's swimpool test at the dose administered (100 mg/kg). Among the synthesized compounds, *N*-(6-fluro-1,3-benzothiazol-2-yl)-2-{[5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetamide (5m) *N*-(6-chloro-1,3-benzothiazol-2-yl)-2-{[5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl]sulfanyl} acetamide (5n) emerged as potent anticonvulsant in both the models (MES and Sc-PTZ), having less, CNS depressant affect in comparison to standard drug carbamazepine. The structure–activity relationship (SAR) showed that the phenyl group with electron withdrawing substitution appeared to have increased anticonvulsant activity. Replacement of phenyl ring with pyridine nucleus further increased the anticonvulsant activity of the compounds.



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SUMMARY
Initial anticonvulsant screening of the compounds was determined by maximal electroshock (MES) and subcutaneous pentylenetetrazole (scPTZ) tests in mice. Most of the compounds were active in the MES and scPTZ tests which is an indicative of their ability to prevent seizure spread. *N*-(6-chloro-1,3-benzothiazol-2-yl)-2-{[5-(pyridine-4-yl)-1,3,4-oxadiazol-2-yl]sulfanyl} acetamide and *N*-(6-fluro-1,3-benzothiazol-2-yl)-2-{[5-(pyridine-4-yl)-1,3,4-oxadiazol-2-yl]sulfanyl} acetamide emerged as the most active compounds having no neurotoxicity and exhibiting less CNS depressant effect.

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PROCEEDING -11

Synthesis and anti-inflammatory and analgesic activity of 4,5-dihydropyrimidine-5-carbonitrile derivatives

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INTRODUCTION
Indole moiety is a known heterocyclic moiety in development of newer, better and safe anti-inflammatory agents after the discovery of indomethacin in 1963. Indole and its derivatives constitute the active class of compounds with wide range of biological activities, such as anti-inflammatory (1), anti-microbial (2) etc.
The purines and pyrimidines are also valuable leads for drug design and discovery due to their key roles in various cellular processes. Pyrimidine and condensed pyrimidine derivatives possessing anti-inflammatory and analgesic activities are well documented in the literature (3). Here we have synthesized a number of pyrimidine derivatives containing indole moiety as one of the substituent and evaluated them for anti-inflammatory and analgesic activities.

EXPERIMENTAL CHEMISTRY
2-Mercapto-4-(1-*H*-indole-2-yl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (**1**): Indole-3-carbaldehyde (1mmol), ethyl cyanoacetate (1mmol) and thiourea (1mmol) were dissolved in absolute alcohol. Potassium carbonate (3mmol) was added and reaction mixture was refluxed for 2hrs. The solution was neutralized with glacial acetic acid, causes the separation of compound **1** which was filtered, washed with water and recrystallized from methanol (Scheme-I).
2-Hydrazinyl-4-(1-*H*-indole-2-yl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (**2**): Compound **1** (1mmol) was dissolved in absolute ethanol and to it hydrazine hydrate (99%; 4mmol) was added and refluxed for 1h. The reaction mixture was allowed to cool which causes the separation of solid. The precipitated product was filtered, washed and recrystallized with ethanol (Scheme-I).
6-(1-*H*-Indole-2-yl)-4-oxo-2-(2-{substituted benzylidene}hydrazinyl)-4,5-dihydropyrimidine-5-carbonitrile (**3-10**): Compound **2** (1mmol) was dissolved in a mixture of glacial acetic acid and alcohol (2:8). To this solution, alcoholic solution of substituted aromatic aldehydes (1.1mmol) were added and refluxed for 5-6hrs. Solvent was

concentrated to half of its volume, poured into ice water. The precipitate obtained was filtered, washed with water and recrystallized from methanol (Scheme-I).

The structures of newly synthesized compounds were characterized by IR, ^{1}H-NMR & mass spectral data.

PHARMACOLOGY: The synthesized compounds were evaluated for their anti-inflammatory activity using carrageenan-induced paw edema volume method of Winter *et al* (4) using indomethacin (10 mgkg^{-1} *p.o.*) as standard.

Analgesic activity was carried out by using acetic acid induced writhing method (5) in Swiss albino mice (25-30g) of either sex using the same standard i.e. indomethacin (10 mgkg^{-1}). A 1% aqueous acetic acid solution (0.1mL) was used as writhing induced agent.

RESULTS AND DISCUSSION

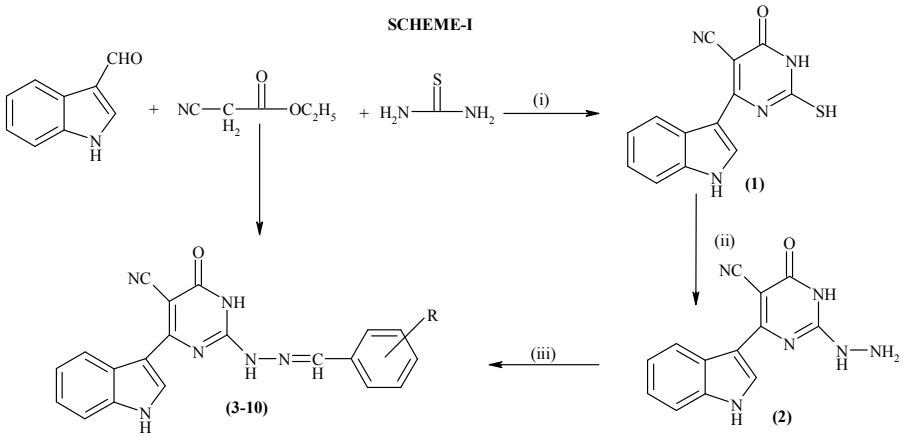
The title compounds, 6-(1-*H*-indole-2-yl)-4-oxo-2-(2-{substituted-benzylidene}-hydrazinyl)-4,5-dihydropyrimidine-5-carbonitrile derivatives (**3-10**), were synthesized by reaction of hydrazine group of 2-hydrazinyl-4-(1-*H*-indole-2-yl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (**2**) with different substituted aromatic aldehydes using a mixture (2:8) of glacial acetic acid and alcohol.

6-(1-*H*-indole-2-yl)-4-oxo-2-(2-{2,4-dichloro-benzylidene}-hydrazinyl)-4,5-dihydro-pyrimidine-5-carbonitrile (**6**) was found to be a good anti-inflammatory and analgesic agent with 69.23% inhibition in edema and 48.26% protection against acetic acid induced writhings.

CONCLUSION

Among the newer derivatives, one compound i.e. 6-(1-*H*-indole-2-yl)-4-oxo-2-(2-{(2,6-dichloro-benzylidene)}-hydrazinyl)-4,5-dihydropyrimidine-5-carbonitrile (**7**) emerged as lead compound having 69.23% inhibition in edema and 48.26% protection against acetic acid induced writhings.

SCHEME-I



Reagents and Conditions: (i) K_2CO_3, Abs. alcohol, reflux; (ii) Hydrazine hydrate, Abs. alcohol, reflux; (iii) Aromatic aldehyde, Glacial acetic acid & Alcohol mixture (2:8), reflux

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PROCEEDING -12

Design, Synthesis and Antihypertensive Activity of Some 7-Substituted-Phenyl-3,4,8,9-tetrahydro-2*H*-pyridazino[1,6-A][1,3,5]triazin-2-thione Derivatives

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INTRODUCTION

Hypertension is a disease, which if left untreated affects all important organs of human body. It is known as silent killer as without showing significant symptoms, it may quietly lead to stroke, brain hemorrhage, cardiac disorders, renal failure and vision loss. Hypertension has affected 10—15% of global population and killed a large number of human race in every region of world. The interesting pharmacological activity displayed by pyridazine derivatives has been demonstrated in recent years not only by the growing number of papers and patents describing them but also by the development of several pyridazine based drugs and pharmacological tools.

EXPERIMENTAL METHODS

Some new 7-substituted-phenyl-3,4,8,9-tetrahydro-2*H*-pyridazino[1,6-a][1,3,5]triazin-2-thione derivatives were synthesized by a sequence of reactions starting from appropriate aryl hydrocarbons as shown in **Figure 1**. All the final compounds were structurally elucidated on the basis of IR, ^{1}H-NMR, ^{13}C-NMR, MS data and elemental analysis. The final compounds were evaluated for antihypertensive activities by non-invasive method using Tail Cuff method.

The *β*-aroyl propionic acid **1** was cyclized on hydrazinolysis to yield 6-(substituted-phenyl)-4,5-dihydropyridazine-3(2*H*)-one **(2a-g)**. Pyridazinone **2** was treated with formaldehyde to give the 2-hydroxymethyl derivative i.e. 2-(hydroxymethyl)-6-(substituted-phenyl)-4,5-dihydropyridazin-3(2*H*)-one (3a-g) which on cyclocondensation with thiourea yielded 7-phenyl-3,4,8,9-tetrahydro-2*H*-pyridazino[1,6-a][1,3,5]triazin-2-one **(4a-g).**

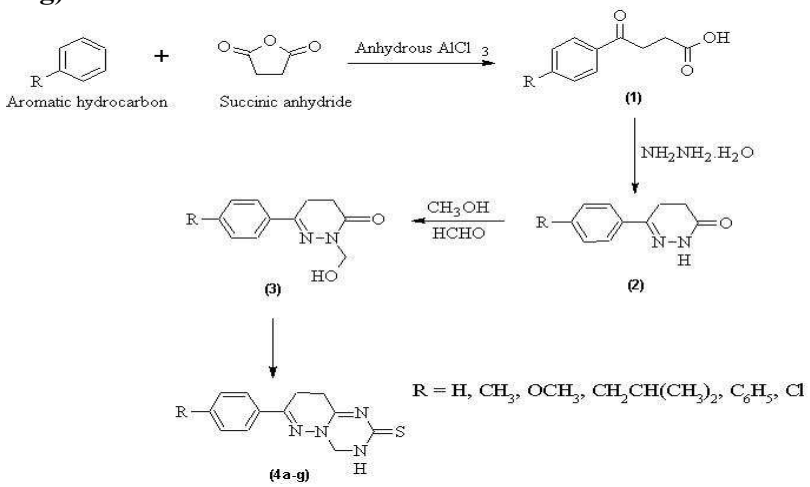

Figure.1

*7-substituted-phenyl-3,4,8,9-tetrahydro-2H-pyridazino[1,6-a][1,3,5]triazin-2-thione deri***vatives**

RESULTS AND DISCUSSION

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The structures of compounds were established by modern analytical techniques: IR, ^{1}H-NMR and Mass spectroscopy. Elemental analysis of compounds was found to be satisfactory and within the range of ±0.4%. All the test compounds showed significant antihypertensive activity, 7-(biphenyl-4-yl)-3,4,8,9-tetrahydro-2*H*-pyridazino[1,6-a][1,3,5]triazin-2-one **(4f)** exhibited antihypertensive activity more than the reference standard drugs. On the basis of activity reported, it can be concluded that groups like *p*-C_2H_5, *p*-$CH_2CH(CH_3)_2$, *p*-C_6H_5 in phenyl ring at 6-position increases the activity.

SUMMARY

All the test compounds showed significant antihypertensive activity, 7-(biphenyl-4-yl)-3,4,8,9-tetrahydro-2H-pyridazino[1,6-a][1,3,5]triazin-2-thione exhibited antihypertensive activity more than the reference standard drugs. The pharmacological effects observed contribute to give information about therapeutic interest of pyridazine derivatives in hypertension.

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PROCEEDING -13

Synthesis and *in-vitro* antimicrobial activity of some novel quinoline based pyrazoles and pyrazoline-5-ones

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INTRODUCTION

Quinolines play a unique role in drug discovery programs. Quinolines for instance, ciprofloxacin, norfloxacin, levofloxacin and moxifloxacin are being marketed as imperative broad spectrum antibiotics for the treatment of microbial infections. Furthermore, various quinoline derivatives are also reported to exhibit a wide spectrum of biological properties such as antimicrobial, antimalarial, and antitubercular activities [1]. Pyrazoles and pyrazoline-5-ones are also important class of heterocyclic compounds showing wide range of biological properties such as antimicrobial, antitubercular and anti-inflammatory activities [2]. Encouraged by these observations and in continuation of our research work on synthesis of heterocyclic compounds we report herein, the synthesis of a hybrid molecules consisting both the quinoline and pyrazole/pyrazoline pharmacophore and highlighted their in vitro antimicrobial activities.

EXPERIMENTAL METHODS

General procedure for the preparation of 3-methyl-4-(2-arylhydrazono)-1-(2-(quinolin-8-yloxy)acetyl)-1H-pyrazol-5(4H)-ones ***3,4(a-j)***. To ethyl-2-(aryl hydrazono)-3-oxobutyrates (**1**)/ aryl-3-diazenyl pentane-2,4-diones (**2**) (0.005 mole) dissolved in glacial acetic acid (20 ml), a solution of 8-quinolinoxyacetic acid hydrazide (0.005 mole) in glacial acetic acid (25 ml) was added and the mixture was refluxed for 3-5 h. It was then cooled and allowed to stand overnight. The resulting solid was dried and crystallized from EtOH/ MeOH. *4-(2-(3-methyl-5-oxo-1-(2-(quinolin-8-yloxy)acetyl)-1H-pyrazol-4(5H)-ylidene)hydrazinyl) benzoic acid* ***3(a)****:* Yield 80%, mp 298 °C; IR (KBr): 3410 (N-H), 1690 (C=O), 1590 (C=N); ^{1}H NMR (300MHz, DMSO-d_6) δ 2.16 (s, 3H, CH_3), 3.34 (s, 2H, OCH_2), 7.30-8.26 (m, 10H, ArH), 11.52 (s, 1H, NH), 12.40 (s, 1H, COOH). MS: 431 [M^+]. Anal. calcd. for $C_{22}H_{17}N_5O_5$: C, 61.25; H, 3.97; N, 16.20. Found: 61.21; H, 3.95; N, 16.23%.

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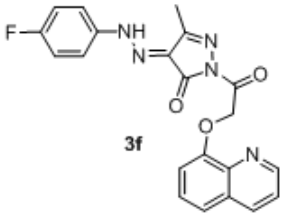
RESULTS AND DISCUSSION

Antimicrobial activity of the synthesized compounds were determined against *Staphylococcus aureus* (ATCC-25923), *Escherichia coli* (ATCC-25922), *Aspergillus niger* (ATCC-9029) and *Candida albicans* (ATCC-90028) by serial plate dilution method at 200 µg/mL, 100 µg/mL, 50 µg/mL, 25 µg/mL, 12.5 µgmL and 6.25 µg/mL concentrations. Ciprofloxacin and ketoconazole were used as reference drugs for comparison [3]. In antibacterial screenings, compounds **3a** (Log *P* 1.32) and **4g** (Log *P* 4.44) bearing carboxyl and chloro substituent at para position of phenyl ring, respectively showed excellent MIC of 6.25 µg/mL against gram positive *S. aureus*. In antifungal screenings, compound **3d** and **4d** having *p*-methoxy group in the phenyl ring showed moderate antifungal activity against *C. albican* (MIC 12.5 µg/mL). Rests of the compounds were found to be less active in comparison to standard drug ketoconazole. The overall antimicrobial screening results showed that compounds having electron withdrawing group at the phenyl ring of pyrazoline-5-one and pyrazole moiety (**3e, 3f** and **4h**) were more active than compounds having electron releasing substituent. Moreover, it was also found that compounds having electron withdrawing group at para position **3a** were more effective than the compounds having electron withdrawing groups at ortho position **3b**. 4-(2-(4-fluorophenyl)hydrazono)-3-methyl-1-(2-(quinolin-8-yloxy)acetyl)-1H-pyrazol-5(4H)-one **3f** having Log *P* 1.52 was found to be the most active compound of the series showing broad spectrum antimicrobial activities.

SUMMARY

Thus it can be concluded that compounds having a hybrid pharmacophore of quinoline and pyrazoline-5-one/pyrazole seems to enhance the antimicrobial activity. Therefore, such compounds would provide a new opportunity for possible modification of pharmacophoric requirements and future exploitations.



3f

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PROCEEDING -14

Synthesis of Some New 2-(4-(5-Phenyl-4,5-Dihydro-1*h*-Pyrazol-3-Yl) Phenoxy) AcetohydrazideDerivatives and their Biological Activity

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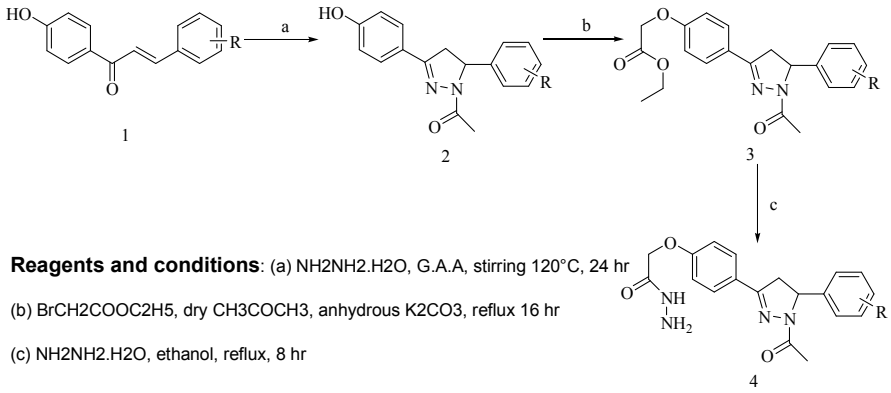
INTRODUCTION:

Diversely substituted pyrazolines and their derivatives embedded with variety of functional groups are important biological agents and a significant amount of research activity has been directed towards this class. Pyrazolines represent an important class of heterocycles due to their highly pronounced biological and pharmacological activities such as antimicrobial, anti-inflammatory, antihypertensive, anticanceractivity.

International Journal of Pharma and Bio Sciences
ISSN 0975 - 6299

Present studywas undertaken in order to synthesize some new pyrazoline and related fused heterocyclic compounds and screen them for anti-inflammatory and analgesic activities.

EXPERIMENTAL:



Reagents and conditions: (a) NH2NH2.H2O, G.A.A, stirring 120°C, 24 hr

(b) BrCH2COOC2H5, dry CH3COCH3, anhydrous K2CO3, reflux 16 hr

(c) NH2NH2.H2O, ethanol, reflux, 8 hr

A. Synthesis of Pyrazoline derivatives was carried out by following the steps mentioned below.
   a. Synthesis of 1-(4-hydroxyphenyl)-3-phenylprop-2-en-1-one (**1**)
   b. Synthesis of 1-(3-(4-hydroxyphenyl)-5-phenyl-4,5-dihydropyrazol-1-yl) ethanone (**2**) from (**1**)
   c. Synthesis of ethyl 2-(4-(1-acetyl-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)phenoxy) acetate (**3**) from (**2**)
   d. Synthesis of 2-(4-(1-acetyl-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl) phenoxy) acetohydrazide(**4**) from (**3**)

B. Anti-inflammatory and Analgesic activity:The anti-inflammatory activity was carried out by rat hind paw edema method and analgesic activity by tail immersion method on albino mice using indomethacin 20 mg/kg (p.o) as standard.

RESULT AND DISCUSSION:

The compounds were successfully synthesized and tested for their biological activity and structure was established by spectral analysis.

Compd	^{1}HNMR ($CDCl_3$)	IR(KBr in cm^{-1}):	MASS m/z
4b	2.38 (3H, s, -$COCH_3$), 3.07 (1H, dd, - CH_2 gem.), 3.70 (1H, dd, -CH_2 gem.), 4.59 (2H, s, -OCH_2), 5.52 (1H, dd, -CH), 6.93 (2H, d, Ar-H), 7.14, 7.18(2H, d, Ar-H) (2H, d,Ar-H), 7.24 (2H, d, Ar-H), 7.75 (1H, bs, -NH, D_2O exchangeable)	3452.73(N-H), 1731.19 (O=C-CH_3), 1669.46 (O=C-N-H), 831.36 (C-Cl)	387.24 $(M+H)^+$
4j	2.41 (3H, s, -$COCH_3$), 3.12 (1H, dd, - CH_2 gem.), 3.7 (1H, dd, -CH_2 gem.), 3.75 (2H, s, -OCH_2), 5.26 (2H, bs, -NH_2), 5.53 (1H, dd, C-H ring),6.82 (2H, d, Ar-H) 7.04 (2H, m, Ar-H), 7.67 (2H, m, Ar-H), 7.7 (2H, d, Ar-H), 8.01 (1H,bs, NH)	3454.73 (N-H), 1734.19 (O=C-CH_3), 1665.46 (O=C-N-H), 837.36 (C-Cl)	m/z 371.40 $(M+H)^+$

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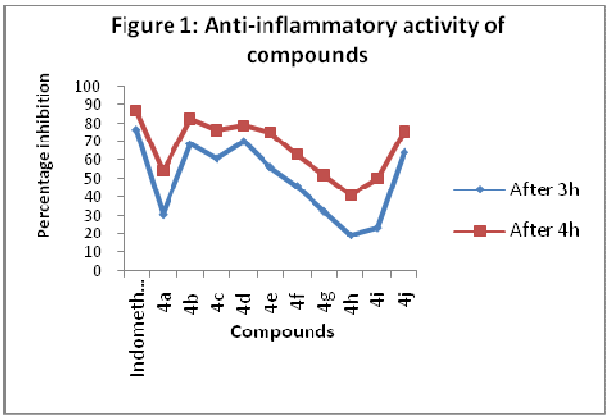
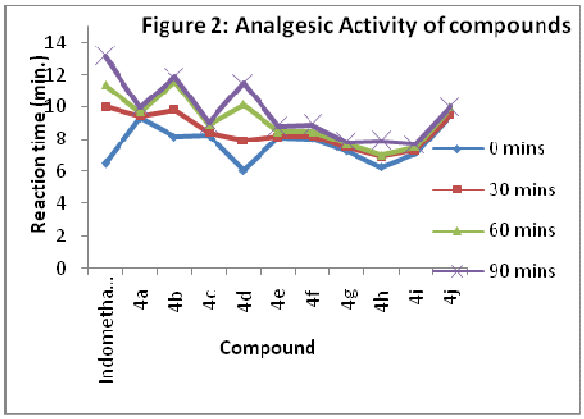
Anti-inflammatory and Analgesic activity:





The present study establishes the anti-inflammatory potential of pyrazoline coupled hydrazides. Anti-inflammatory potential of the compounds can be improved by substituting the more electron withdrawing groups like di-chloro, trifluoro methyl etc, and avoiding bulky groups in the structure.

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PROCEEDING -15

Screening of different natural products influencing Astaxanthin production by *Phaffia rhodozyma* MTCC 7536 using response surface methodology

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INTRODUCTION

Carotenoids are a class of over 600 organic pigments that are ranging from red to orange to yellow color and are used as additives in feed, food, drug and cosmetic industries. Carotenoids belong to the category of tetraterpenoids (i.e. they contain 40 carbon atoms). Carotenoids are produced in the chloroplasts of plants including sweet potatoes, pumpkins, broccoli, kale and carrots (Nancy et al., 2010) and some algae and bacteria.

MATERIALS METHODS

MICROORGANISM: Culture of *Phaffia rhodozyma* MTCC 7536 was obtained from Institute of Microbial Technology (IMTECH), Chandigarh, India.

SUBMERGED FERMENTATION:

All experiments were carried out in 250 ml Erlenmeyer flask containing 50 ml of production medium. Each Erlenmeyer flask was inoculated with 10% of the seed culture and incubated at 20^0C for 5-7 days on a rotary shaker at 200 rpm (Montgomery et al., 1997; Zhu et al., 2005).

EFFECTS OF DIFFERENT NATURAL PRODUCTS ON ASTAXANTHIN

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Different natural products (Beta vulgaris, Calendula officinalis, Capsicum annum, Ipomoea batatas, Solanum lycopersicum, Pennisetum glaucum, Cocos nucifera, Fructose pure, Zea mays, Triticum aestivum, Brassica juncea, Manihot esculanta, Curcuma longa, Triticum aestivum, Whey, Malus domestica, Saucus carota, Papaver somniferum, Allium cepa, Cucurbita pepo, Rosa damascene, Brassica rapa)were added in a concentration of 2 g into reported medium (Glucose 20 g/l, Diammonium sulphate 1 g/l, Potassium dihydrogen phosphate 1 g/l, Magnesium sulphate 0.5 g/l, Calcium chloride 0.1 g/l, Manganese sulphate 0.5 mg/l, Zinc chloride 0.14 mg/l, Ferric chloride 0.27 mg/l, Copper sulphate 1.25 mg/l, Distilled water 1 l) and inoculated with yeast strain and incubated for 7 days under shaking conditions at 200 rpm at 20^0C (Montgomery et al. 1997; Zhu et al., 2005). Finally total carotenoids concentration, biomass, and free astaxanthin concentration was extracted and analyzed.

OPTIMIZATION OF ASTAXANTHIN PRODUCTION BY RESPONSE SURFACE METHODLOGY

Four medium components: marigold, maize, maida, and bajra were chosen for study. An experimental design of 29 runs containing 5 central points was made according to Box-Behnken's response surface design for selected four parameters using DESIGN EXPERT 7.1.6 software. An experimental design of 29 runs containing 5 central points was made according to Box-Behnken's for selected parameters using DESIGN EXPERT 7.1.3 software (Inc. USA) to screen these medium parameters. The individual and interactive effects of these nutrient parameters were studied during fermentation. The response was measured in terms of actual factors of free astaxanthin production.

RESULTS AND DISCUSSION

The carotenoids that affects maximum to the astaxanthin bioaccumulation are marigold (24.76 total carotenods mg/g of yeast, 6.0928 µg/ml free astaxanthin, 0.678 g/ml biomas), bajra (32.39 total carotenods mg/g of yeast, 5.6554 µg/ml free astaxanthin, 0.627 g/ml biomas), maize (24.09 total carotenods mg/g of yeast, 5.9777 µg/ml free astaxanthin, 0.667 g/ml biomas) and maida (19.99 total carotenods mg/g of yeast, 5.5633 µg/ml free astaxanthin, 0.603 g/ml biomas).

The analysis of variance of calculated model for frees astaxanthin production, ANOVA for model terms of Response Surface Quadratic Model and Stastical Data of Response surface model of free astaxanthin (**Table 1**). Point prediction tool of DESIGN EXPERT 7.1.6 software was used to determine the optimum values of the factors for maximum free astaxanthin production. Finally, the optimum values of marigold 2.5 g/l, maize 2.38 g/l, maida 1.89 g/l and bajra 2.47 g/l resulted in a free astaxanthin 1405.65 µg/l.

Table 1**.**

ANOVA for model terms of Response Surface Quadratic Model.

Source	Free astaxanthin				
	Sum of squares	df	Mean square	F-value	p-value Prob > F
Model	4687441	14	334817.2	9.882061	< 0.0001**
X_1	796.2552	1	796.2552	0.023501	0.8803
X_2	18756.19	1	18756.19	0.553585	0.4692
X_3	40298.43	1	40298.43	1.1894	0.2939
X_4	32125.37	1	32125.37	0.948174	0.3467
$X_1 X_2$	51804.04	1	51804.04	1.528986	0.2366
$X_1 X_3$	1445.901	1	1445.901	0.042675	0.8393
$X_1 X_4$	27560.98	1	27560.98	0.813457	0.3824
$X_2 X_3$	4.5369	1	4.5369	0.000134	0.9909
$X_2 X_4$	257.763	1	257.763	0.007608	0.9317
$X_3 X_4$	9332.526	1	9332.526	0.275448	0.6079

X_1^2	1613669	1	1613669	47.62712	< 0.0001**
X_2^2	1024293	1	1024293	30.2318	< 0.0001**
X_3^2	1691778	1	1691778	49.93248	< 0.0001**
X_4^2	2568585	1	2568585	75.81126	< 0.0001**
Residual	474338.4	14	33881.31		
Lack of fit	387210.4	10	38721.04	1.777662	0.3046
Pure error	87128	4	21782		
Cor. total	5161779	28			

SUMMARY: Among all the tested caretenods and other natural products marigold, maize, maida, and bajra effect maxium to astaxanthin bioaccumulation. The optimum concentration of these resulted 1405.65 µg/l of free astaxanthin by *Phaffia rhodozyma* MTCC 7536.

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PROCEEDING -16

Synthesis and Anticonvulsant evaluation of some new derivatives of Thiobarbituric acid

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INTRODUCTION

Worldwide, epilepsy is a major health problem affecting about 1.5-2% of the population in developing countries, and 0.8-1.3% in developed countries. Presently available anticonvulsant (antiepileptic) drugs are effective in controlling the seizures, but they are associated with various side effects like sedation, hypnosis and so on, thereby disturbing day time work. Research for an ideal anti-epileptic drug which control seizures without causing significant side effects is still the need of the millennium.

EXPERIMENTAL METHODS

Recent literature showed that heterocyclic and bi-heterocyclic compounds have emerged as structurally novel anticonvulsants. Thiobarbituric acid (2-Thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione) and indole derivatives have acquired conspicuous significance as anticonvulsants in recent years. Therefore, keeping in mind the potential of both these moieties and as a part of our work on diazines, the present study was carried out, wherein a series of 1,3-bis(substituted phenyl)-5-(1*H*-indol-3-ylmethylidene)-2-thioxodihydro pyrimidine-4,6(1*H*,5*H*)-dione derivatives **(IIIa-g)** has been synthesized by Knoevenagel condensation of Indole-3-carbaldehyde with the N,N-disubstituted thiobarbituric acid in ethanol using piperidine as a base.

The structures of newly synthesized compounds were characterized by IR, ^{1}H-NMR & mass spectral data. All the synthesized compounds were evaluated for their anticonvulsant activity using two most adopted seizure models, maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (scPTZ) in mice.

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- **MAXIMAL ELECTROSHOCK SEIZURE (MES)**

Albino mice were stimulated through corneal electrodes to 50 mA current at a pulse of 60 Hz applied for 0.2 s. Animals were previously treated with the test drug i.p. Abolition of hind limb tonic extension spasm was observed as the anticonvulsant activity. Polyethylene glycol (PEG) was used as control. In the preliminary screening, each compound was administered as an i.p. injection at three dose levels (30, 100 and 300 mg/kg) and the anticonvulsant activity assessed after 0.5 h and 4.0 h intervals of administration.

- **PENTYLENETETRAZOLE-INDUCED SEIZURE TEST**

The subcutaneous pentylenetetrazole test was used according to the method of Clark *et al*. Pentylenetetrazole (70 mg/kg) that produces seizures in tested animals as a 0.5% solution subcutaneously in the posterior midline. After 2–4 min of PTZ injection animals developed the sequence of excitement, myoclonic jerks, clonic seizures, one or more maximal tonic seizures. The animal was observed for 30 min; Absence of clonic spasm in half or more of the animals in the observed time period indicated a compound's ability to abolish the effect of pentylenetetrazol on seizure threshold.

- **NEUROTOXICITY SCREENING**

The minimal motor impairment was measured in mice by the rotarod test. The mice were trained to stay on an accelerating rotarod of diameter 3.2 cm that rotates at 10 rpm. Neurotoxicity was indicated by the inability of the animal to maintain equilibration on the rod for at least one minute in each of the three trials. The dose at which 50% of the animals enabled to balance themselves and fell off the rotating rod was determined.

RESULTS AND DISCUSSION

Among the tested derivatives, some of the compounds showed significant protection against MES induced convulsions at 100 mg/kg but none of the compound found protective against PTz induced convulsions.

SUMMARY

Anticonvulsant activity results of the designed derivatives demonstrated that the synthesized compounds were found protective in MES model as compared to subcutaneous PTz model.

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PROCEEDING -17

One-Pot Synthesis of Substituted Carbohydrazides as Potential Tuberculostics

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INTRODUCTION

Tuberculosis (TB) remains a leading infectious cause of death worldwide, but very few new drugs have been approved for TB treatment in the past 37 years, despite recent efforts. The current drug therapy for TB is long and complex, involving multidrug combinations (usually isoniazid, rifampin, ethambutol, and pyrazinamide for the initial two months and rifampin and isoniazid for an additional four months). The need for such lengthy treatment is largely because the drugs are relatively ineffective against the persistent form of the disease.

EXPERIMENTAL METHODS

International Journal of Pharma and Bio Sciences
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A series of 6-oxo-3-substituted-phenyl-5,6-dihydropyridazine-1(4*H*)-carbohydrazides (**2a-g**) has been synthesized as shown in **Figure 1**. An appropriate aromatic hydrocarbon reacts with succinic anhydride in presence of anhydrous $AlCl_3$ to yield *β*-aroyl propionic acid. The corresponding acid was cyclized with 1,3-diamino urea by refluxing in absolute ethanol in presence of sodium acetate to get the final compounds.

SYNTHESIS OF NEW SUBSTITUTED 6-OXO-5,6-DIHYDROPYRIDAZINE-1(4*H*)-CARBOHYDRAZIDE DERIVATIVES

To a solution of β-benzoylpropionic acid (0.01 mol) in absolute ethanol (30 mL) were added carbohydrazide (0.01 mol) and sodium acetate, and the mixture was refluxed for 6 h. After completion of the reaction, ethanol was distilled off and the residue was poured into cold water. The solid which separated was filtered and washed with water. The product was dried in air and crystallized from ethanol.

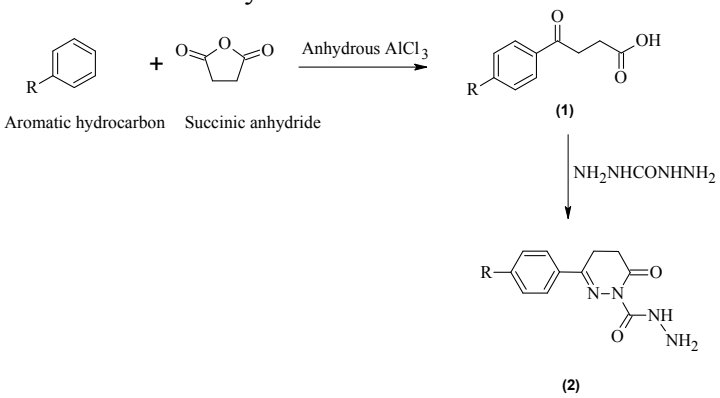

Figure 1.
Synthesis of new substituted 6-oxo-5,6-dihydropyridazine-1(4H)-carbohydrazide derivatives

RESULTS AND DISCUSSION

All the final compounds were structurally elucidated on the basis of IR, ^{1}H-NMR, ^{13}C-NMR, MS data and elemental analysis. The newly synthesized compounds were screened for their *in vitro* anti-tubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$ using the BACTEC 460 radiometric system.

SUMMARY

All the newly synthesized compounds were showing moderate to high inhibitory activities, with compound **2g** produced was found to be the most promising compounds active against *M. tuberculosis* $H_{37}Rv$ and isoniazid (INH) resistant *M. tuberculosis* with Minimum inhibitory concentration 0.10 and 0.10 µM.

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PROCEEDING -18

Pharmacophore mapping of sulfotransferase inhibitors using V-life software

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INTRODUCTION

Sulfated biomolecules mediate a wide array of normal and pathological cellular events. For example, sulfated carbohydrates arbitrate leukocyte adhesion to inflamed endothelium, sulfated proteins modulate HIV-1 infectivity, and sulfation also regulates the activity of steroid hormones *in vivo*. The role of sulfated biomolecules in numerous diseases has prompted the search for inhibitors targeting the enzymes that install sulfate esters, the sulfotransferases. Sulfotransferases catalyze the transfer of a sulfuryl group from 3'-phosphoadenosine 5'-phosphosulfate (PAPS) to a hydroxyl (or amino) group on a carbohydrate,4 protein, or small molecule acceptor. The strong connection between sulfotransferases and several disease states has prompted interest in the discovery of potent and selective sulfotransferase inhibitors both as tools to elucidate the role of these enzymes *in vivo* and as potential therapeutics.

A pharmacophore model represents the 3D arrangements of the structural or chemical features of a drug that may be essential for interacting with the protein for optimum binding.

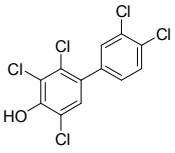
These pharmacophore models can be used differently in drug design programs such as

(i) 3D query tool for virtual screening to identify potential new compounds from 3D databases of "drug-like" molecules that have patentable structures different from those that currently exist

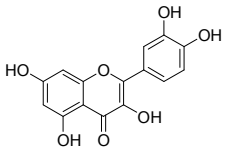
(ii)Tool to predict the activities of a set of new compounds that remain to be synthesized.

MATERIALS AND METHODS

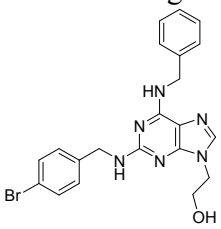
The MolSign module in VLifeMDS provides tools for aligning small organic molecules based on their three dimensional pharmacophore features. All calculation was conducted on VlifeMDS^{TM} 3.5, installed in Windows operating system. Molecules were edited using the Chem/3-D visualizer.



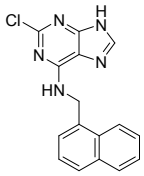
1
IC_{50} (0.15-0.25 nM)



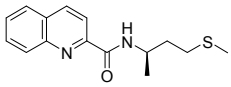
2
IC_{50} (0.1 μM)



3
IC_{50} (20 μM)



4
IC_{50} (96 μM)

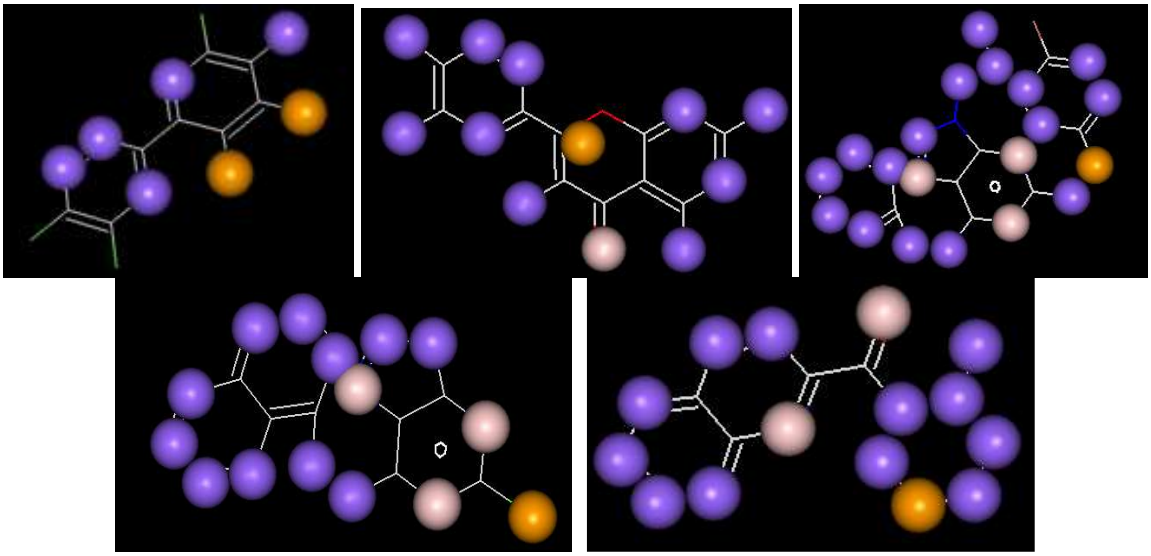


5
IC_{50} (30 μM)

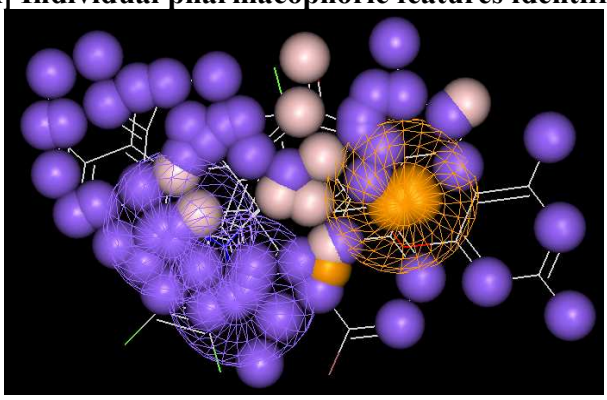
Dataset selected for generation of pharmacophore model

RESULTS & DISCUSSION

From the above dataset we have generated different biophore [**A**] of 5 molecules, which were aligned to make a common pharmacophore model [**B**]. This model contains three features named AlaC NegC and NegC which will be used for searching the database of millions compounds.



[A] Individual pharmacophoric features identified



[B] Common pharmacophore points

The larger tessellated spheres are indicative of the common pharmacophores identified in the molecules, the smaller solid features are of the individual molecules.

SUMMARY:

1. Structure interaction fingerprints was used to prioritize the screened compounds which makes it possible to quickly shortlist potential active leads using clustering.
2. The structural models of ligands will facilitate further medicinal chemistry efforts in search and rational design of more potent sulfotransferase inhibitors.

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PROCEEDING -19

Synthesis of new 1,2,4-triazolo[3,4-*B*][1,3,4]thiadiazole derivatives and their microbiological evaluation

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INTRODUCTION

An anti-microbial is a substance that kills or inhibits the growth of microorganisms such as bacteria, fungi, or protozoans. Antimicrobial drugs either kill microbes (microbiocidal) or prevent the growth of microbes (microbiostatic). The 1,2,4- triazolo thiadiazole ring play a central role in numerous molecules of established bioactivities, which includes fungicidal,insecticidal,bactericidal,herbicidal, anti-tumor, anti-inflammatory, CNS stimulant properties. A triazolo-thiadiazole system may be viewed as a cyclic analog of two very important components—thiosemicarbazide and biguanide, which often display diverse biological activities.

EXPERIMENTAL METHODS

A series of 1,2,4-triazolo[3,4*b*][1,3,4]thiadiazole derivatives **(Va-d)** were synthesized and evaluated for their antimicrobial activity. 3-substituted 4-amino-5-mercapto-1,2,4-triazoles were cyclised with different aromatic acids in the presence of phosphorous oxychloride to yield 3-substituted-6-aryl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles derivatives. The structures of synthesized compounds were confirmed on the basis of their elemental analysis and spectral data results. Gram positive(Staphylococcus aureus) and Gram negative(Escherichia coli) bacterial strains and fungi(Spergillus flavus) were used.Antimicrobial activity of compound is evaluated by cup plate method.The plates were kept in cold for one hour to allow the diffusion of test compounds and then incubated at 37+-0.5 degree Celsius for 24 hours for antibacterial activity and 48 hours for antifungal activity respectively.The zone of inhibition formed around the cups after respective incubation was measured and percentage inhibition of the compounds were evaluated.

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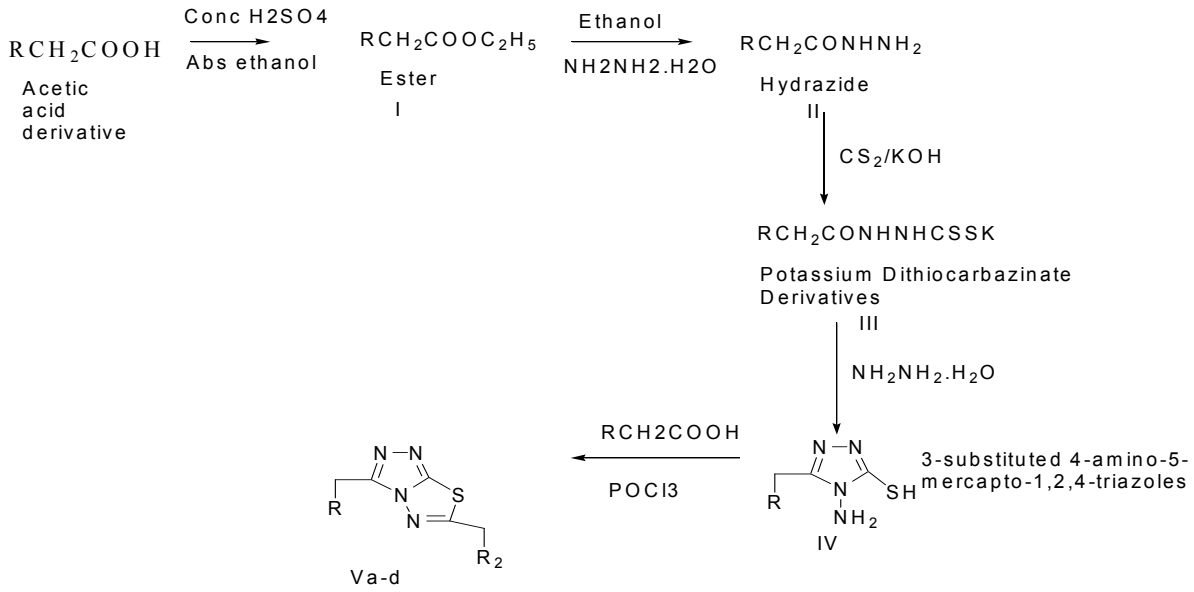

R=$C_{12}H_9CH_2$- , $(C_6H_5)_2CH$- , C_6H_5-O -C_6H_4-CH_2-
R_2=C_6H_5CO $NHCH_2$-, 2-BrC_6H_4-, 3 -BrC_6H_4-, 4-BrC_6H_4-,
2-C_6H_5CO -C_6H4- , $C_8H_5NHCH_2$-, $C_{10}H_7CH_2$- , C $_6H_5COCH_2CH_2$-

RESULTS AND DISCUSSION

The solution of the compounds was prepared in dimethyl sulfoxide in a conc of 100ug/ml,200ug/ml and 300ug/ml.Cup plate method was used for evaluation of antimicrobial activity.The zone of inhibition formed around the cups was measured and percentage inhibition of the compounds was evaluated with reference to the standard drugs.Compound **Vb** showed highest activity against *S.aureus* with 68.75% inhibition.Rest of the compounds showed moderate activity against both *S.aureus* and *E.coli*.Compound **Va** showed activity with 57.89%inhibition against *Spergillus flavus.*

SUMMARY

The synthetic route involved the synthesis of 1,2,4-triazole derivatives followed by condensation with different aromatic acids in POCl3 to give novel 3,6-disubstituted-1,2,4-triazolo(3,4-b)[1,3,4]thiadiazole derivatives.The antimicrobial activity was done by cup plate method on *S.aureus,E.coli* and *Spergillus flavus* using Ofloxacin and Fluconazole as standard drugs.Compound **Vb** showed highest activity against *S,aureus* at 200ug/ml.Against fungus *Spergillus flavus* compound **Va** showed activity with 57.89% inhibition.

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PROCEEDING -20

Aegle marmelos: A New Herbal Approach for the treatment of Diabetes Mellitus and its Complications

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INTRODUCTION

Diabetes mellitus is a metabolic syndrome which is spreading like wildfire. According to WHO fact sheet, 346 million people are suffering from diabetes. It was estimated that by 2030, the diabetic death will double from 2005 (i.e. 3.4 million).Increased oxidative stress is an important player in the development and progression of diabetes and its complications. Oral hypoglycaemic agent used in its treatment includes many side effects. Herbal drugs are free from such side effects. *Aegle marmelos* (L.) Corr. is a herbal drug, belonging to family Rutaceae is a popular medicinal plant in the Ayurvedic and Siddha systems of medicine and folk medicines used to treat a wide variety of ailments.The plant, popularly known as the bael tree, is native to the Indo-Malayan region. *Aegle marmelos* was evaluated for its efficacy against diabetes and its complication.

EXPERIMENTAL METHODS

PREPARATION OF AQUEOUS EXTRACT OF *AEGLE MARMELOS*LEAVES (AML).

Aegel marmelos leaves were thoroughly washed in water and dried in shade. Fifty grams of air dried leaves were grounded into fine powdered and then soaked in water for 7-8 hours, stirred occasionally. After soaking mixture was filtered using whatman no. 1 filter paper. The filtrate was centrifuged at 10,000 rpm at room temp and supernatant was collected. Supernatant was collected upto 100 ml on rotavapour under reduced pressure. The concentrated crude extract was be lyophilized into powder was used for study.

ANIMAL

Forty eight male wistar albino rats (3 months old) were procured from central animal house facility, Jamia Hamdard New Delhi. Animals were housed in polypropylene cages maintained under ideal laboratory conditions (12-h light/ 12h dark cycle; 25±3ºc; 35-60% humidity).they were fed on standard pellet diet and water *ad libitum* throughout the experimental period. The animal use protocol was reviewed and approved byInstitutional Animal Ethics Committee (IAEC), Jamia Hamdard, New Delhi.

PREPARATION OF DIABETIC MODEL

Animal were divided into six groups each comprising of 8 animals (I) vehicle treated group, (II) diabetic control group, (III) AML *per* se group, (IV) AML250mg/kg treated group, (V) AML500 mg/kg treated group, (VI) Gliclazide 25mg/kg treated group.After acclimatization of 4-5 days, type-2 diabetes mellitus was induced (except group I and III) serving as control group in overnight fasted animal by single i.v injection of 40mg/kg of streptozotocin dissolved in 0.05 M citrate buffer, (pH 4.5). After induction of NIDDM the animal models were standardized through glucose tolerance test.Different doses of AML were given for 21 days. During the treatment and after the treatment various biochemical parameters were estimated.at the end of experiment animal was sacrificed and organs was isolated for histopathological examination.

RESULTS AND DISCUSSION

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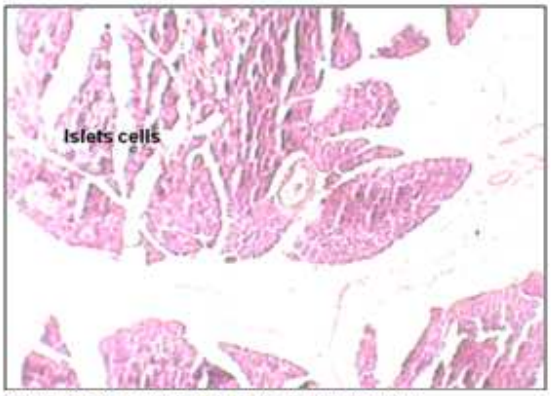
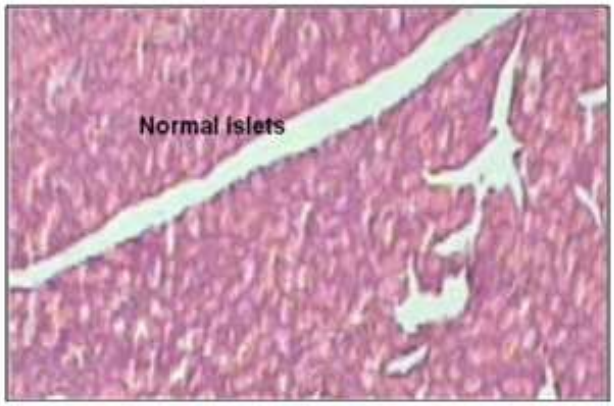
In the present study anti-hyperglycaemic effect of AMLdose of 250 and 500mg/kg were 138.97 ± 5.81 and 103.31 ± 6.71 respectively and comparable to that of standard oral hypoglycaemic agent Gliclazide(79.74 ± 4.39). Oral glucose tolerance test (OGTT) for normal control, and diabetic experimental groups were done. In diabetic control rats the peak increase in glucose level was observed after 1 hour and remained higher. While AML (190.56 ± 5.84and 166.29 ± 12.53) and Gliclazide (144.26 ± 13.05) treated rats showed significant decrease in blood glucose level. ThusAML increases the glucose tolerance. AML and Gliclazide showed significant decrease in HbA1c level at all doses.It indicates that AML decreases the glycosylation process.A marked increase in the concentration of TBARS has been observed in STZ diabetic rats3.53 ± 0.24.The decrease in the level of TBARS was observed in the pancreas of treated animals1.51± 0.23&0.90 ± 0.14 may be due to the inactivation of the lipid peroxidation.A marked decrease in the concentration of reduced glutathione has been observed in STZ diabetic rats 2.16 ± 0.1, and AML at all doses 3.28 ± 0.32 &4.77 ± 0.31 significantly increase the reduced glutathione level. It indicates that AML prevented the oxidative stress in STZ diabetic rats.Histopathological examination reveals that these were consistent with those of biochemical studies and normalization of pancreatic islets size with more pronounced effect at higher dose of AML (500 mg/kg).



Group II Toxic control (STZ 40 mg/kg) Pancreas :10x
Figno 1: Low Power photomicrograph ofpancreas from animal given STZ only showing reduction and atrophy of pancreatic isletcells (HE x 100)



Group VIII: STZ + AML 500 mg/kg Pancreas :10x,
Figno2: showing pancreatic tissue with increased and normal sized islet of Langerhans (HE x 100)

SUMMARY

These results demonstrated AML has antihyperglycaemic and antioxidant effects in STZ induced diabetic rats, suggesting that AML can be useful in preventing diabetic complications with oxidative stress.

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PROCEEDING -21

Development and characterization of transdermal microemulsion for Alendronate.

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INTRODUCTION

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Osteoporosis is a disease affecting post-menopausal women and elderly men, characterized by either increased bone resorption or diminished bone formation or both. Alendronate is classified as a biphosphonate which plays a major role in bone density management. But previous studies have shown that the oral bioavailability of alendronate is very low (0.6-0.7%) and further gets reduced when taken with meals. Hypothesis of the present study is that transdermal microemulsion (ME) of alendronate, when applied on skin surface, would permeate the skin due to its nanometric droplet size. This would alleviate the bioavailability issues associated with oral administration [1, 2].

EXPERIMENTAL METHODS

PREPARATION OF MES:

Determination of Solubility of Alendronate in Oils, Surfactants and Co-surfactants: The solubility of alendronate in various oils, surfactants, co-surfactants was determined. An excess amount of alendronate was added in 2ml of the selected oil, surfactant and co-surfactant and they were kept in mechanical bath shaker for 72h at 37^{o}C. The equilibrated samples were centrifuged at 10,000 rpm for 10 min. The supernatant was separated, filtered and analysed for drug content.

Construction of Pseudo-Ternary Phase Diagram: In order to optimize surfactant and co-surfactant, phase diagrams for each surfactant and co-surfactant combinations were constructed by using aqueous titration method.

Thermodynamic Stability of MEs: MEs were subjected to a) Heating cooling cycle, b) Centrifugation, c) Freeze thaw cycle and d) Dispersibility Test.

CHARACTERIZATION OF MES: *Droplet Size and Size Distribution:* Droplet size was determined by photon correlation spectroscopy that analyzed the fluctuations in light scattering due to brownian motion of the particles, using a Zetasizer.

CYTOTOXICITY ANALYSIS

Vero cell-line (1X10^{5}cells/ml) maintained in DMEM and 10% FBS were plated in 96-well plate and incubated at 37C with 5% CO_2 for 24hrs. Cells were treated with different concentrations of alendronate and incubated for 48hrs. 20µl of MTT prepared in D-PBSA was added to each well and again incubated for 4hrs. 200µl of DMSO was added into each well to terminate the assay. Readings were taken at 570nm using an ELISA plate reader. Percentage viability was calculated.

RESULTS

*Solubility studies***:** Maximum solubility of alendronate was observed in Clove oil (oil phase), Tween 80 (surfactant) and ethanol (co-surfactant).

Preparation of MEs and construction of pseudoternary diagrams Care was taken to ensure that observations were not made on metastable systems. At Smix 5:1 and 6:1, maximum ME area was observed.

*Thermodynamic Stability studies of Drug loaded MEs***:** Out of all the emulsions which were tested for stability, two emulsions remained stable after all the stability tests

Characterization of MEs: The pH of the MEs came out to be 6.5 to 7.0. The average particle diameter sizes was 17.78nm with PDI of 0.125.

Cytotoxic Analysis: MEs of alendronate were found to have no cytotoxic effects on Vero cell lines till 10-8M concentration after 48 hrs treatment.

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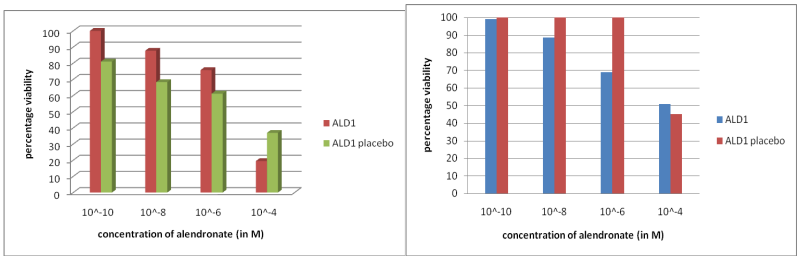

(a) **(b)**

Figure.1.

Cell viability after treatment with alendronate loaded and corresponding placebo MEs for (a) 24hrs and (b) 48 hrs, respectively.

SUMMARY

Stable oil-in-water MEs of alendronate were successfully prepared for the transdermal delivery. MEs were found to be non-toxic to normal Vero cells.

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PROCEEDING -22

EFFECT OF RUTIN AND PYRITINOL ON SELENITE-INDUCED CATARACT IN RAT PUPS

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INTRODUCTION

Cataract is a growing menace globally. Surgery although an effective means of reversing cataract has not however, eliminated the problem because of many reasons (Haque and Gilani, 2005). Though a new long term initiative to expand the capabilities of cataract surgery and service levels with financial assistance from the World Bank has been undertaken, alternative means to slow down the advancement of the disease by prophylactic means is a desirable goal (Haque and Gilani, 2005). Thus, it is appropriate to search for a drug, which can prevent or delay cataract formation. Experimental evidences suggest that oxidative stress due to accumulation of free radicals play an important role in pathogenesis of cataract (Spector, 1995). In the present study we have evaluated the anticataract property of Rutin and Pyritinol, which are strong antioxidants (Morel et al., 1993; Pavlik et al., 1989), in selenite-induced cataract in Wister Albino rat pups. Sodium selenite induces cataract formation when administered to young rats before completion of the critical maturation period of the lens at approximately 16 days of age (Shearer et al., 1997)

EXPERIMENTAL

Wistar Albino rat pups, housed together with their mother, were taken for this study.

The mother rat was fed on normal diet and water ad libitum. The pups were suckled by their mother. The pups were divided into four groups. Group I received nothing, Group II received single subcutaneous (s.c.) dose of selenite (30 µmol/kg, b.w.) on 10^{th} day of life, Group III and IV received single s.c. dose of selenite (30 µmol/kg, b.w.) on 10^{th} day along with Rutin (80 mg/kg, b.w) and Pyritinol (100 mg/kg, b.w) intra-peritonealiy

(i.p.), respectively for two consecutive days, i.e., 10th and 11th day of life. The eyes of pups were opened on 15th postnatal day. Development of cataract was observed by torchlight and ophthalmoscope up to the 30th day. Cataract was developed in all pups. Pups were sacrificed on 30th day. Lenses were removed from the eyes of all groups for the estimation of lens soluble protein (Lowry et al., 1951), reduced glutathione (Ellman, 1959) and lens water content (Gupta and Joshi, 1994).

RESULTS

The lens protein level of sodium selenite treated animals (Group II) showed a significant ($P<0.01$) decrease as compared to the normal control group (Group I). Rutin (Group III) and Pyritinol (Group IV) showed a significant increase ($P<0.01$, respectively) in lens protein as compared to toxic control (Group II).

The lens glutathione level of sodium selenite treated pups (Group II) showed a significant ($P<0.01$) decrease as compared to normal control group (Group I). Rutin (Group III) and Pyritinol (Group IV) showed a significant increase ($P<0.01$, respectively) in lens glutathione as compared to toxic control (Group II).

The lens water content of sodium selenite treated pups (Group II) showed a significant ($P<0.01$) decrease as compared to normal control group (Group I). Rutin (Group III) and Pyritinol (Group IV) showed a significant increase ($P<0.01$, respectively) in lens water content as compared to toxic control (Group II).

DISCUSSION

The strong antioxidant property of Rutin and Pyritinol play a key role in their anticataract activity. The underlying mechanism is attributed to the decrease of soluble protein level in toxic control group under oxidative stress created by sodium selenite (David et al., 1993b). Under this condition the protein gets denatured and forms disulphide and mixed disulphide bond leading to protein aggregation and precipitation, hence lens opalescence. The situation is however improved along with an increase in the protein level in rat pups treated with Rutin and Pyritinol.

The induction of cataract and its prevention by these drugs is also indicated by the lens reduced glutathione level. Here the lens reduced glutathione level of sodium selenite treated group is less than that of control, which is again increased with the administration of Rutin and Pyritinol. As the oxidative stress increases, the reduced glutathione level decreases in order to combat with the situation to prevent oxidative damages (Haque and Gilani, 2005). The situation here again is indicated improved with the administration of these drugs. The preventive role of these drugs has also been substantiated by the estimates of lens water content which is increased on treatment with Rutin and Pyritinol.

CONCLUSION

Our results thus indicate that Rutin and Pyritinol show a preventive role in Selenite induced cataract in rat's pups.

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PROCEEDING -23

Evaluation of antidepressant effects of celecoxib (COX 2 inhibitor) and its combination with duloxetine (SNRI) in stressed mice

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INTRODUCTION

In recent years, a potential link between inflammation and depression has been shown and the role of pro-inflammatory cytokines in the pathophysiology of major depressive disorders has been observed. Celecoxib (selective COX 2 inhibitor) has been reported to inhibit the production of PGE-2 and pro-inflammatory cytokines and also increase tryptophan levels and serotonin availability in depressed patients. On the other hand, duloxetine (potent SNRI) has been shown to be efficacious in inflammatory and acute pain models in rodents and synergistic interaction with NSAIDs. However, the interactions of duloxetine with celecoxib are currently unknown.

EXPERIMENTAL METHODS:

Male swiss albino mice weighing 25-35g, were procured from the Central Animal House Facility, Jamia Hamdard, New Delhi. They were randomized into 8 groups, including the naive group, where animals received vehicle for 15 days without forced swimming session; the control (chronically stressed) group where mice received vehicle 30 min before the forced swimming session (6mins) for 15 days. Drugs were suspended in 0.25% CMC and administered ip, 30mins before the forced swimming session for 15 consecutive days. After 15 days, various behavioral assessments followed by biochemical estimation were conducted, on the subsequent day 16^{th}.

Following parameters were assessed:

BEHAVIORAL

Tail suspension test (TST): The mouse was suspended by the tail and total duration of immobility was calculated for a period of 6 mins (Steru et al, 1985).

Locomotor activity: Animal was kept in photoactometer for the first 3 min and then locomotor activity was recorded using photoactometer foe a period of 5 min. the apparatus was placed in darkened, light-sound attenuated and ventilated testing room (Reddy and Kulkarni, 1998).

BIOCHEMICAL

Thiobarbituric acid reactive substances (TBARS) estimation (Ohkawa et al., 1979)

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Glutathione estimation (Ellman, 1959)

RESULT AND DISCUSSION

Pretreatment of celecoxib (15, 30 mg/kg) for 15 days to forced swim-induced stressed mice produced significant antidepressant effect which has been evidenced by decreased in immobility time in tail suspension test (TST). Celecoxib (30 mg/kg) also showed significant increase in locomotor activity and protective effect on biochemical parameters of oxidative stress by reversing stress-induced increase in TBARS and reduction in GSH levels. Pretreatment with combination of celecoxib with duloxetine (5, 10 mg/kg) showed significant antidepressant and neuroprotective effects against stress induced depression and oxidative damage in mice at both dose levels.

CONCLUSIONS: This study demonstrated dose-dependent antidepressant action of celecoxib in stressed mice. The combination of celecoxib with duloxetine further enhanced its antidepressant effect on TST in stressed mice. The treatment reversed forced swim-induced elevation in TBARS levels and depleted glutathione activity, suggesting their antioxidant and protective role in brain.

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PROCEEDING -24

Thermodynamics as a tool to study pharmaceutical processes

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INTRODUCTION

Low solubility associated with a reduced dissolution rate often becomes a rate-limiting step in absorption of poorly water-soluble drugs. This is attributed to the fact that the driving force for the passive absorption is supposed to be the concentration gradient across the biological membrane. Compounds with an aqueous solubility lower than 100 µg/ml present dissolution limitations to absorption [1]. Here an attempt has been made to study the influence of different solid states (crystalline, semi crystalline and amorphous) on physical properties like solubility (aqueous, organic and lipidic), partition coefficient of a problematic drug (Itraconazole) by different thermal treatments.

EXPERIMENT AND METHODOLOGY

Bulk Itraconazole was obtained as a gift sample from Jubilant organosys, Noida (India). All chemicals and reagents used were of analytical, HPLC and UPLC-MS grade whatever required and were purchased from Merck (Mumbai), India.

PHYSICAL TREATMENTS TO BULK DRUG

Bulk drug was subjected to the following treatments to create changes in the crystal lattice of Itraconazole.

Sample A. Bulk Itraconazole. It remained untreated and served as a control.

Sample B. 5 grams of Itraconazole were exposed to hot metal plate at 180°C (above the melting point) for 15 minutes.

Sample C. 5 gram of Itraconazole was dissolved in 100 ml of dichloromethane in a conical flask and sonicated for 5 minutes. It was poured immediately over metallic plate (previously heated above 100° C) for 30 seconds and then placed immediately inside refrigerator at -20° C. After 5 minutes it was removed from the refrigerator and placed in vacuum oven at 40°C to remove the moisture adsorbed.

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Sample D. 5 gram of Itraconazole was dissolved in 100 ml of dichloromethane in a conical flask and sonicated for 5 minutes. It was poured over china dish and placed over water bath that allows the solvent to evaporate slowly. Obtained solid sticky mass was allowed to cool at room temperature and then passed from 100 mesh sieve to get a fine powder.

2.2 CHARACTERIZATION OF DIFFERENT SOLID STATES

Different solid states were characterized by Differential scanning calorimetry, Powder X ray diffraction, Molecular dynamics simulation studies. Fourier transforms infrared spectroscopy Mass spectroscopy and Residual solvent content.

2.3 SOLVATION CHARACTERISTICS

2.3.1 AQUEOUS SOLUBILITY

Excess of Itraconazole (Samples A, B, C and D) was added to 10 ml aqueous solution (pH 1). The samples were shaken, centrifuged, filtered and then analyzed by slight modification into reported LC-MS/MS method [1]. The standard solution Gibbs energies were calculated using following equation:

$\Delta G^{\circ}_{sol} = -RT \ln X_2$,

2.3.2 DETERMINATION OF DRIVING FORCES OF SOLUBILISATION

Different aqueous solutions with variable pH (1-4) were made by addition of drops of concentrated HCl into 100 ml of Milli Q water. Excess amount of all different samples (A, B, C and D) were added into different solution and solubility (25°C) was determined.

2.3.3 DETERMINATION OF PARTITION COEFFICIENT

A biphasic system, acetate buffer (pH 4.5)/ octanol were taken to determine partition coefficient of samples (A, B, C and D). The fraction of moles in both the immiscible fluids was taken to calculate various thermodynamic parameters.

RESULTS-

DSC, Powder XRD, Molecular dynamics simulation studies, FT IR, MS and Residual solvent content indicated the formation of different solid states of the bulk drug maintaining the integrity of the molecule. The exhaustive results of solubility and partition coefficient studies present here some interesting results.

Table 1

Thermodynamic parameters of solubilisation process of A, B, C and D in aqueous solution at variable pH (1, 2 and 4) at 25° C.

Samples	pH	Solubility (µg/ ml)	Mole Fraction	ΔG^{298}_{sol} (kJ mol^{-1})	ΔH^{298}_{sol} (kJ mol^{-1})	$T\Delta S^{298}$ sol (kJ mol^{-1})	ΔS^{298}_{sol} (J mol^{-1} K^{-1})
A	1	24.17±2.3	0.618×10^{-6}	35.42	55.3±1.5	19.88	66.71
	2	0.55±4.1	0.014×10^{-6}	44.79	35.6±1.5	-9.19	-30.83
	4	0.13±3.7	0.00335×10^{-6}	48.33	44.5±0.8	-92.83	-311.51
B	1	35.97± 6.9	0.927×10^{-6}	34.40	40.2±1.9	5.8	19.46
	2	2.95±2.4	0.0760×10^{-6}	40.60	55.1±1.1	10.92	36.64
	4	0.695±5.1	0.0179×10^{-6}	44.18	37.3±0.9	-6.88	-23.08
C	1	57.23± 3.4	1.47×10^{-6}	33.26	48.8±1.1	15.54	52.14
	2	7.76±5.6	0.2001×10^{-6}	38.20	31±0.9	-7.2	-24.16
	4	2.49±6.4	0.0642×10^{-6}	41.02	47.3±0.7	6.28	21.07
	1	28.26± 3.6	0.728×10^{-6}	34.83	56.2±2.1	21.37	71.71

D	2	9.71±5.3	0.2504× 10^{-6}	37.65	29.2±1.8	-8.45	-28.35
	4	0.93±2.4	0.0239× 10^{-6}	43.46	28.8±1.3	-14.66	-49.19

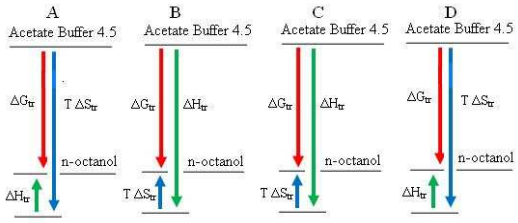

Figure 1:

Schematic representation of driving forces during partitioning between Acetate buffers (pH 4.5) to n-octanol. Experiment was carried out at room temperature (298K) and in a triplicate mode.

CONCLUSION

The current research work ensures the formation of an amorphous state of a highly crystalline but thermo-stable substance by employing new controlled heat methods without using any other excipient. Such systems were then evaluated for solubility and partition coefficient. The methods used for preparing them were also compared. These parameters were also studied in terms of thermodynamics (ΔG, ΔH and ΔS). Driving forces of different solid states prepared by the various physical processes were found to be changing according to their chemical potential and free energy available.

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PROCEEDING -25

SIGNIFICANCE OF COMBINATORIAL CHEMISTRY IN DRUG DISCOVERY FROM NATURAL PRODUCTS

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In drug discovery after successful identification and development of target and testing system, the next job is to find a lead compound. Today with so many targets being discovered, Pharmaceutical industries are faced with the problem of finding lead compounds as quickly as possible. Combinatorial techniques have been developed to synthesize a large number of molecules in short time by condensing the starting materials in all possible combination following a defined reaction route. Here emphasis is to produce a mixture of compounds, whose structures are not known with certainty. Compounds are neither separated nor purified. Mixture called combinatorial library is tested for biological activity as whole. If activity is there, then move for identification of active entity[1]. Using 3 different CD-rings, 4 different A-rings and 6 different side chains, a vitamin D_3 library of 72 discrete compounds have been produced. In case of epothilone using 3 building-blocks and a ring closing metathesis reaction for macrocyclization combinatorial, a library of the complex natural products has been obtained, allowing study of QSAR on a relevant level. Biological approach has been applied for synthesis of

vinca alkaloids. Genes for tryptophan decarboxylase and strictosidine synthase has been isolated from *Catharanthus roseus* and cloned in *Staphylococus cereviseae*. After feeding tryptamine and secologanine, strictosidine and its aglycone were biosynthesized in *S. cereviseae*.

INTRODUCTION

Drug discovery as a whole is very complex, tedious and costly process, where more than 100 disciplines work together. Disease and target selection, lead compound finding, metabolism and toxicity studies and clinical trials are some of the stages of drug discovery. Many of these stages run concurrently and are dependent on each other. After successful identification and development of target and testing system, the next job is to find a lead compound. Today with so many target being discovered, pharmaceutical industries are faced with a problem of finding a lead compounds as quickly as possible. Pharmaceutical industries might expect to carry out lead discovery against 100 target per year for which there will be need to screen over millions of compounds. The success of screening depends on the availability of compounds, as well as their quality. There are many ways of finding lead compound. Combinatorial library is one the excellent source for finding lead compound in drug discovery[1].

VITAMIN D

The 11-hydroxy analogues of vitamin D have been synthesized by attaching the 11-hydroxy function of the CD-ring system to diethylsilyl polystyrene followed by installation of the A-ring by a Horner–Wadsworth–Emmons (HWE) reaction and the side chain by a Cu(I) mediated Grignard reaction. For library production, the CD-ring system was immobilized to the resin by a side chain sulfonate linker, which allowed installation of different side chains by Grignard following the HWE reaction. Using three different CD-rings, four different A-rings and six different side chains, a library of 72 discrete compounds was produced using a radiofrequency-encoded synthesis strategy[2].

EPOTHILONES

These macrocyclic polyketides are obtained from myxobacteria and have anti-mitotic activity. Selective oxidations-reductions of epothilones, as well as cleaving the thiazole moiety and substituting it with other aromatic and heteroaromatic rings have been achieved[3,4]. Also, oxidations, reductions and acid-catalyzed rearrangements of the macrocyclic ring were achieved. Of the many variations towards synthesis of epothilone derivatives, both in solution and solid phase, the traceless linking of the epothilones in SMART micro reactors is noteworthy. The key step is the simultaneous formation and release of the lactone macrocycle from the resin by a ring-closing metathesis reaction[4,5]. Because many substituents cannot be introduced late in the synthesis.

VINCA ALKALOIDS

Vinblastine and Vincristine are monoterpenoid-indole alkaloids from *Catharanthus roseus*, (Apocyanaceae) used as antineoplastic agent. The plant has extreme low yield (3 mg/kg). Production of vinca alkaloids in plant cell cultures did not lead to a significant. In whole biosynthesis at least 30 biosynthetic and 2 regulatory genes are involved, which encode around 35 intermediates[6]. Genes for tryptophan decarboxylase and strictosidine synthase has been isolated from *C. roseus* and cloned in *S. cerevisiae.* After feeding, tryptamine and secologanin, strictosidine and its aglycon were biosynthesised in *S. cereviseae.* When strictosidine glucosidase was additionally over expressed in the recombinant host *S. cereviseae* carrying the tryptophan decarboxylase and strictosidine synthase gene, a sufficient amount of strictosidine was formed. The cDNA coding for strictosidine synthase from *Rauwolfia serpentina* has been expressed in *E. coli* and in insect cells and was found to convert secologanin and tryptamine into strictosidine[7].

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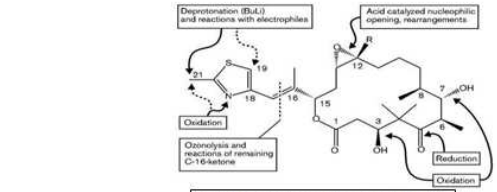
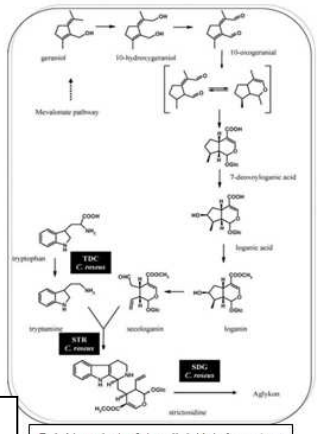


Structure of epothilone A (R = H) and B (R = Me)



Early biosynthesis of vinca alkaloids in *S. cerevisiae*

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PROCEEDING -26

RECENT ADVANCES IN THE UNDERSTANDING OF DEPRESSION

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INTRODUCTION: Depression is one among the most rampant form of psychiatric disorders and a leading cause for morbidity and mortality[1]. Depression should be recognized as a clinical syndrome that is characterised by a cluster of emotional, behavioural, and cognitive features. Depression is a common problem affecting about 121 million people world-wide. It occurs in persons of all genders, ages, and back- grounds[1]. Depression is almost

twice as common in females as males. Depression is associated with a serious impairment of social, marital, and occupational functioning, as well as prominent personal and interpersonal distress[1].

CLINICAL SIGNS AND SYMPTOMS: Depression refers to a wide range of mental health problems which is characterized by enduring sadness, anhedonia (Loss of interest or pleasure in almost all activity), guilt, low self esteem, disturbed sleep, poor appetite, low energy, a lack of libido, fatigue, poor concentration & reduced attention, pessimistic and suicidal tendencies[1].

PATHOPHYSIOLOGICAL FEATURES OF DEPRESSION: Clinical evidence supports the fundamental roles of serotonin and norepinephrine, as well as the interactions between these systems in the etiology of depression. In addition, corticotropin-releasing factor, dopamine, GABA, somatostatin, substance P and thyroid-related hormones have been implicated in the pathophysiology of depression[2,3].

1. MONOAMINES: All three monoamines (5-HT, NE, & DA) are important in the regulation of mood, emotion, and cognitive function. Many of these functions have been demonstrated to be impaired in patients with depression. MAO is enzyme protein responsible for metabolizing monoamines like NE, DA & 5-HT. MAO-A has substrate preference for serotonin and is the main target for the antidepressant monoamine oxidase inhibitors (MAOIs). MAO-B has substrate preference for phenylethyl amine. Both enzymes act on nor-adrenaline and dopamine. In case of depression the level of monoamine oxidase enzyme in brain is increased which in turn reduce the levels of monoamines. Noradrenergic cell bodies in the brainstem (lateral tegmental area & locus coeruleus) give rise to diverse projections to a variety of brain structures. The NE released following activation of noradrenergic neurons mediates effects through interaction with alpha and beta adrenoceptors. The effects of serotonin are mediated through 5-HT receptors.In patients with depression, an increased density of postsynaptic 5-HT2 receptor binding sites has repeatedly been reported in both frontal cortex and platelets. Dysfunction in the serotonergic system is a well-established theory explaining the pathophysiology of depression. Dopaminergic neurons therefore innervate brain areas associated with behavioral & physiological functions that are altered in depression (e.g., the cortex, limbic structures & pituitary gland[2,3].

2. GABA: GABA is a major inhibitory neurotransmitter in brain. GABA-B agonists may enhance cAMP responses to nor-adrenaline and β-adrenergic down-regulation in response to tricyclic antidepressants suggesting a facilitative role for GABA-B. GABA levels have been reported to be decreased in the CSF of depressed patients in some studies[3].

3. CORTICOTROPIN-RELEASING FACTOR: CRF is a hypothalamic hypophycotropic factor that controls the release of corticotropin from the anterior pituitary gland. In turn, corticotropin stimulates the adrenal cortex to release hormones essential for the organism's response to stress (glucocorticoids & mineralocorticoids). In addition to this neuroendocrine role, CRF plays a central role in coordinating the behavioral, autonomic, and immune responses to stress. Indeed, CRF is present in a variety of extrahypothalamic brain regions (the locus coeruleus & amygdala, which suggests a role for CRF in mood disorders[2]. People with depression also exhibit elevated basal levels of both cortisol and CRF[2,3]. Thyroid hormones provide feed back to both the hypothalamus and pituitary to regulate the axis. CSF TRH was increased in two small studies of depressed patients[2].

4. BDNF & INFLAMMATORY CYTOKINES : BDNF is found in blood, where it mostly accumulates in platelets. Interestingly, several studies have found decreased blood levels of BDNF in depressed patients[1,3]. Depressed patients have been found to have higher levels of pro-inflammatory cytokines, acute phase proteins, chemokines & cellular adhesion molecules[2].

NEURAL CIRCUITRY OF DEPRESSION: Brain imaging has identified numerous regions of altered structure or activity in the brain during major depression, suggesting disordered neurocircuitry in a variety of structures, such as the anterior & posterior cingulate cortex; the ventral, medial, and dorsolateral prefrontal cortex; the

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ISSN 0975 - 6299

insula; the ventral striatum; the hippocampus; the medial thalamus; the amygdala; and the brain stem. These brain areas regulate emotional, cognitive, autonomic, sleep, and stress-response behaviors that are impaired in mood disorders[1,2].

CONCLUSION: Depression is associated with a serious impairment of social, marital, and occupational functioning, as well as prominent personal and interpersonal distress. Depression is a common disorder that affects quality of life, productivity, and healthcare outcomes.

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PROCEEDING -27

HERBAL NUTRACEUTICAL

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Nutraceuticals is a food or part of a food that provides medical or health benefits including the prevention and / or treatment of a disease. Nutraceutical has advantage over the medicine because they avoid side effect, have naturally dietary suuplement, etc. Nutrceutical ;on the basis of their natural source, chemical grouping. categories into three key term –nutrients, herbals, dietary supplements, dietary fiber etc. The most rapidly growing segments of the industry were dietary supplements (19.5 percent per year) and natural/herbal products (11.6percent per year). Global nutraceutical market is estimated as USD 117 billion. FDA regulated dietary supplements as foods to ensure that they were safe. . In 2006, the Indian government passed Food Safety and Standard Act to regulate the nutraceutical industry. Herbal nutraceutical as a powerful instrument in maintaining health and to act against nutritionally induced acute and chronic diseases, thereby promoting optimal health, longevity and quality of life.

INTRODUCTION

The term nutraceuticals was coined from "nutrition" and "pharmaceutical" by Stephen Defelice MD, founder and chairman of the foundation for innovation in medicine (FIM) Cranford, NewJersy in 1989[Brower v. 1989]. According Defelice nutracetuicals is a food or part of a food that provides medical or health benefits including the prevention and / or treatment of a disease[Trottier, G., 2010] Greek physician HIPPOCRATES (known as father of medicines) said "let food be your medicine" The philosophy behind is" focus on prsevention"

Simply, Nutraceuticals means, ***NUTRITIVE +PHARMACEUTICAL****: a food stuff(as a fortified food or dietary supplement) that provides health benefits.*

HEALTH BENEFITS

- Avoid the side effect .
- May increase the health beneficial effect
- May have naturally dietary supplement so do not have unpleasant side effect.

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- May increase the health value our diet and improve medical condition of human
- May easily available n economically affordable [Jian Zhao 2004]

CATEGORY OF NUTRACEUTICAL

- Substances with established nutritional functions, such as vitamins, minerals, amino acids and fatty acids – **Nutrients.**
- Herbs or botanical products as concentrates or extracts –**Herbals.**
- Reagents derived from other sources (e.g. pyruvate, chondroitin sulphate, steroid hormone precursors) serving specific functions, such as sports nutrition, weight-loss supplements, fortified conventional foods and meal replacements – **Dietary supplements.**

GLOBAL DEMAND OF NUTRACEUTICAL

- The nutraceutical industry lies under three main segments include functional foods, dietary supplements, and herbal/natural products[Rishi RK 2006] .
- Global nutraceutical market is estimated as USD 117 billion (INR5148 billion) [Ernst & Young 2009].

REGULATIONS

FDA regulated dietary supplements as foods to ensure that they were safe and wholesome and that their labeling was truthful and not misleading.

GOVERNMENT REGULATIONS – NLEA 1990

Nutrition Labeling and Education Act of 1990 (NLEA) defines how food is labeled, including nutrition labeling, in accordance with definitions established by FDA, and providing for the use of claims about the relationship between nutrients and diseases or health-related condition.

COMMON HERBALS AS NUTRACEUTICALS

S.No	COMMON NAME	BIOLOGICAL NAME	CONSTI - TUENT	HEALTH BENEFITS
1.	Garlic	Dried bulbs of *Allium sativum* (Liliaceae).	Allin & allicin	Antinflammatory , antibacterial, antigout, nervine tonic
2.	Maiden hair tree	Leaves of *Ginkgo biloba (Ginkgoaceae).*	Ginkgolide & bilobalide	PAF antagonist, memory enchancer, antioxidant

List of marketed nutraceutical products

S.no.	Product	Category	Contents	Manufacturer
1.	Calcirol D-3	Calcium supplement	Calcium and vitamins	Cadilla healthcare limited, Ahmedabad, India
2.	GRD	Nutritional supplement	Proteins, vitamins, minerals and carbohydrates	Zydus Cadila Ltd. Ahmedabad, India

CONCLUSION

Nutraceuticals have proven health benefits and their consumption (within their acceptable Recommended Dietary Intakes) will keep diseases at bay and allow humans to maintain an overall good health.

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PROCEEDING -28

Drug Discovery and Development: An Overview

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INTRODUCTION:
The processes of new drug discovery and development are long, complicated and dependent upon the expertise of a wide variety of scientific, technical and managerial groups. Therefore, it is a scientific endeavor that is highly regulated because of legitimate public health concerns. The three major phases in drug development include pre-clinical research and development; Clinical research and development; and after the compound is in the market, a possible post-marketing phase.

PRE-CLINICAL TESTINGS:
It is done to evaluate the acute and short term toxicity in animals and to determine lethal dose thus assessing how drug is being absorbed, distributed, metabolized and excreted out in animals. The pre-clinical phase represents bench (in vitro) and then animal testing, including kinetics, toxicity and carcinogenicity.

CLINICAL TRIALS:
The compounds that resist rejection at the preclinical stage and deserve trial in humans are approached to the regulatory authorities who on satisfaction issue an investigational new drug (IND) license. The clinical research (IND) phase includes 4 phases:

Phase I trials, sometimes called, "first in human" trials, are generally conducted on relatively small groups (typically 10 to 30) of healthy volunteers (except for oncology drugs or other potentially toxic compounds) in specialized units resembling small hospitals with 20 to 50 monitored beds. It includes the initial introduction of an investigational new drug into human.

Phase II trials are conducted at specialized centers, like university medical centers, by specialized investigators and aimed at elucidating dose response relationships, safety and, for the first time, efficacy, of the compound treating the disease or condition for which it is intended. Drug-drug interactions are also studied carefully during this Phase in diseased patients.

Phase III studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained in Phase 2 and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug. When the pivotal trials are proved efficacious and safe, then all data—pre-clinical and clinical—is compiled into an NDA for submission to regulatory agencies. The NDA includes an integrated summary of efficacy (ISE) and of safety (ISS).

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Phase IV trials are also known as Post-marketing surveillance. Even when an NDA is approved, regulatory scrutiny of a drug does not end. Post-marketing trials are conducted to answer specific additional efficacy or safety questions. If safety concerns arise, the FDA may demand withdrawal of a drug from the market at any time, for an instance (terfenadine {Seldane®}, cisapride {Propulsid®}, and cervistatin {Baycol®}.

CONCLUSION:

The journey of a drug from a molecule to its formulation encompasses various steps from pre-clinical to clinical trials to assess safety and efficacy, to determine dosage, adverse events and additional post marketing side effects are evaluated by the regulatory bodies.

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PROCEEDING -29

Biotransformation of lignans

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INTRODUCTION

Lignans belongs to the category of phytoestrogens which are: SECO (Secoisolariciresinol), MAT (Matairesinol), PINO (Pinoresinol) and their glycosides, HMR (Hydroxymatairesinol) , LCS (Lariciresinol) and isoLCS (isolariciresinol). They are converted into mammalian lignans, Enterodiol and enterolactone {END and ENL}by intestinal microbes aerobically as well as anaerobically (2). Mammalian lignans have been reported to exhibit weak estrogenic and antiestrogenic activity. As none of the single-colony bacterial strains could produce END, the biotransformation is conducted jointly by several different bacteria.

There are several advantages of biotransformation of lignans to mammalian lignans (2).

a) Lignans are used as the substrate for END production. No extra carbon source is needed in the culture, because the most energy- efficient carbon sources e.g. Glucose, normally repress the utilization of other energy source by microorganisms.
b) The use of aerobic bacteria, for END production without the need of strictly anaerobic conditions make large scale production much easier.
c) END and ENL can be produced by chemical synthesis, which is expensive, leads to environmental pollution and very complex requiring more than ten major steps. Moreover the chemicals used in synthesis include $LiAlH_4$ and CH_3OH which are toxic and harmful to the environment.
d) In biotransformation, the solvent used are only water and ethanol, both of which could be recycled.

The metabolic processes of precursors to ENL and END by intestinal bacteria include deglucosylation, demethylation, ring cleavage, dehydroxylation, and oxidation of diols to γ-butyrolactones. Reactions are enantioselective and interconversion between the respective enantiomers did not occur during bacterial metabolism.

POSSIBLE PATHWAY FOR BIOTRANSFORMATION OF LIGNANS TO MAMMALIAN LIGNANS.

PINO converts to LCS by *Eggerthella lenta* by means of ring cleavage. Further LCS undergoes ring cleavage by same organism to form SECO.

SECO can also be formed by deglucosylation of SDG by *Bacteroides* or *Clostridium* sp.

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SECO then converts to END via two step process:
a) *Demethylation by Peptosteptococcus species* of (+) SECO to (+) dihydroxy enterodiol.
b) Dehydroxylation by Eggerthella species of (+) dihydroxy enterodiol to (+) enterodiol.
Then END gets converted to ENL via intermediate enterolactol through dehydrogenation by *Lactonifactor longoviformis*.
MAT can also get converted to ENL via demethylation followed by dehydroxylation by *Peptostreptococcus species* and *Eggerthella species* respectively (2).
IsoLCS was stable during incubation and was not metabolized as easily as other lignans. LCS was reported to be extensively converted to mammalian lignans (5).

CONCLUSION

Biotranformation is a very economic, efficient, and eco-friendly way of mass producing END from lignans.

ABBREVIATION

END:	Enterodiol.	SDG:	Secoisolariciresinol diglucoside.
ENL:	Enterolactone.	SECO:	Secoisolariciresinol.
MAT:	Matairesinol.	PRS:	Pinoresinol.
LCS:	Lariciresinol.		

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PROCEEDING -30

Antileishmanial agents from medicinal plants

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INTRODUCTION

Leishmania are kinetoplastid protozoan parasite responsible for a spectrum of diseases collectively known as leishmaniasis. Twenty species are known to infect humans and cause four main clinical syndrome – cutaneous leishmania , mucocutaneous leishmania, visceral or kala azar, diffuse. Leishmania is prevalent in tropical and temperate regions of the world and continues to be one of the six entities on WHO tropical disease list. There is growing number of reports of leishmania/HIV co infection, which is highly prevalent in Mediterranean basin. Current treatment of the disease is based on a limited number of synthetic chemotherapeutic agents like antimonials, amphotericin B, etc., which are readily becoming ineffective because of emergence of resistance and are characterized by high toxicity and cost. Natural products obtained from plants possess significant activity against leishmania species.

ALKALOIDS

Quinoline alkaloids 2-n-propylquinoline, chimanine-D and B isolated from *Galipea longiflora* (Rutaceae) exhibit antileishmanicidal activity against *L.braziliensis* promastigotes.
Gabunine , a bisindole alkaloid obtained from stem bark of *Pescheira van heurkii* (Apocynaceae) exhibits in vitro activity against *L.amazonensis* amastigotes.

FLAVONOIDS

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Luteolin and quercetin isolated from *Vitex negundo* (Verbenaceae) and *Fagopyrum esculentum* (Polygonaceae) are potent antileishmanicidal compounds against *L.donovani*

CHALCONES

Licochalcone A, an oxygenated chalcone isolated from chinese liquorice *glycyrrhiza spp* (Fabaceae) exhibits strong antileishmanicidal activity markedly preventing growth of *L.major* & *L.donovani* promastigotes and amastigotes.

IRIDOIDS

Amarogentin, a secoiridoid glycoside isolated from *Swertia chirata* (Gentianaceae) is a potent topoisomerase 1 inhibitor. Niosomal formulation reduced the splenic parasite load by 90%

SAPONINS

Six oleane triterpenoid saponins mesabalides 1-6 derived from *Maesa balansae* (Myrsinaceae) showed strong leishmanicidal activity.Administration of purified extract containing saponins reduced the parasite burden of the liver by 95% in a BALB/c mice model one day after infection.

LIGNANS

Diphyllin isolated from *Haplophyllum bucharicum* (Rutaceae) showed anti leishmanicidal activity against *L. Infantum* promastigotes and intracellular amastigotes.

SESQUITERPENE

Artemisinin isolated from *Artemisia annua* (Asteraceae) triggers cell cycle arrest and induces apoptosis.

MONOTERPENE

Linalool, a monoterpene extracted from *Croton cajucara* exhibits strong anti leishmanicidal activity against *L. Amazonensis* promastigotes and amastigotes.

COUMARINS

The coumarin isomers 2-epicycloisobrachycoumarinone and cycloisobrachycoumarinone isolated from *Vernonia brachycalyx* (Asteraceae) display selective activity against promastigotes of *L. major.*

FUTURE PROSPECTIVES

Despite the advances in the parasitological and biochemical researches using various species of leishmania, the treatment options available for leishmania are far from satisfactory. Natural products are potential sources of new and selective agents for treatment of protozoan. It is of great importance to probe the active principles of antileishmanicidal agents for subsequent target based drug design. From a chemical point of view, derivatization of identified lead structures and evaluation of essential binding structures will contribute to improving efficacy and specificity to the parasite.

CONCLUSION

It can be concluded that leishmania is a poorly investigated disease and is a problem in developing countries. Therefore it offers less commercial incentive to pharmaceutical companies to develop cheap and effective drug .Hence poor people rely on traditional system of medicinewhich are cheap and readily available. The tremendous chemical diversity offered by natural products gives a promising approach for treatment of leishmaniasis.

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International Journal of Pharma and Bio Sciences
ISSN 0975 - 6299

PROCEEDING -31

OPTIMIZABLE EXTRACTION TECHNIQUES FOR NATURAL PRODUCTS

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The economic impact of plant based extracts especially for food, nutraceuticals, cosmetics, flavors/fragrances and pharmaceutical industry has grown in the last years. Phytochemicals are extracted by using soxhlet, microwave, ultra-sonic, supercritical carbon dioxide assisted and pressurized liquid extraction techniques. All these methods are optimizable that can be standardized for different parameters using Response Surface Methodology (RSM).

INTRODUCTION

Response Surface Methodology (RSM) is a collection of mathematical and statistical techniques useful for the modeling and analysis of problems in which a response of interest is
influenced by several variables and the objective are to optimize this response (Montgomery 2005). Many experimental programs are designed with a two-fold purpose in mind: to quantify the relationship between the values of some measurable response variable(s) and those of a set of experimental factors presumed to affect the response(s) and, to find the values of the factors that produce the best value or values of the response(s).

Response surface methodology (RSM) consists of a group of mathematical and statistical techniques used in the development of an adequate functional relationship between a response of interest, y, and a number of associated control (or input) variables denoted by $x1, x2, \ldots, xk$. In general, such a relationship is unknown but can be approximated by a low-degree polynomial model of the form

$$y = f'(x)\beta + \varepsilon \qquad (1)$$

where $x = (x1, x2, \ldots, xk)'$, $f(x)$ is a vector function of p elements that consists of powers and cross- products of powers of $x1, x2, \ldots, xk$ up to a certain degree denoted by d (≥ 1), β is a vector of p unknown constant coefficients referred to as parameters, and ε is a random experimental error assumed to have a zero mean. This is conditioned on the belief that model (1) provides an adequate representation of the response.

Response Surface Methodology (RSM) is used for the optimization of different parameters of extraction such as solvent composition, type of solvent, temperature, pressure for the extraction methods like soxhletion, microwave, ultra-sonic, supercritical carbon dioxide assisted and pressurized liquid extraction.

SOXHLETION it is used for the exhaustive extraction of phytochemicals. It is simple and economic extraction technique.

MICROWAVE-ASSISTED EXTRACTION (MAE) has been used as an alternative to conventional methods in the extraction of organic compounds from plant materials and foods. It is based upon the selective and rapid localized heating of moisture in the sample by microwaves. MAE is also applied to several samples simultaneously; therefore time of extraction is reduced dramatically.

ULTRASOUND ASSISTED EXTRACTION (UAE) process deals with the extraction of oil, protein and bioactives from plant and animal materials (e.g. polyphenolics, anthocyanins, aromatic compounds, polysaccharides and functional compounds) with increased yield of extracted components, increased rate of extraction, achieving reduction in extraction time and higher processing throughput. Ultrasound can enhance existing extraction processes and enable new commercial extraction opportunities and processes.

SUPERCRITICAL CARBON DIOXIDE (SFE) assisted extraction provides several operational advantages over traditional extraction methods. Due to their low viscosity and relatively high diffusivity, supercritical fluids

have better transport properties than liquids, can diffuse easily through solid materials and therefore allow to obtain higher extraction yields.

PRESSURIZED LIQUID EXTRACTION (PLE) is a new extraction technique that uses organic solvents at high pressures and temperatures above their normal boiling point. With PLE, a solid sample is packed into a stainless steel extraction cell and extracted with a suitable solvent under elevated temperature and pressure.

CONCLUSIONS: Response Surface Methodology (RSM) used for the optimization of different parameters for extraction for the above mentioned extraction techniques.

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PROCEEDING -32

NDM-1: AN INDIAN SUPERBUG

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INTRODUCTION

NDM-1 is a New Delhi Metallo β-Lactamase essentially found in Enterobacteriaceae (principally E. coli and K. pneumoniae). Itis a novel metallo-β-lactamase (MBL) conferring resistance to almost all β-lactam antibiotics, including carbapenems, recently identified in Klebsiellapneumonia and Escherichia coli isolates from a Swedish patient who travelled to New Delhi, India in 2008.Subsequent growing incidence of NDM-1 strains in India, Pakistan, Bangladesh and now turning up in Britain and many other countries around the world and UK (totally 180 bacterial isolates mostly found among Escherichia coli and Klebsiellapneumoniae) has been reported in the Lancet recently. The Lancet Infectious Diseases triggered a media storm and brought the public's attention to the world's newest superbug when 37 strains of NDM-1 were found in the UK and 99 strains alone were found in India.The rapid spread and dissemination of these multidrug-resistant (MDR) bacteria worldwide represents amajor public health problem, thus the US Centers for Disease Control and Prevention (CDC) has recently planned to add NDM-1-producing MDR bacteria as agents of communicable diseases, and hospitals must immediately report any suspect cases, particularly those for which the patient received medical treatmentin India or Pakistan.The gene that encodes for NDM-1 has been found on plasmids. Plasmids are small segments of genetic material that are easily transferred from one bacterium to another. The organism was non-susceptible to imipenem and other beta-lactam antibiotics, aminoglycosides and co-trimoxazole.

KEY MEASURES FOR PREVENTION ARE:-

- Increased screening (particularly all patients transferred from overseas hospitals).
- Isolation of carriers and reinforced hygiene measures.
- Careful use of antibiotics.
- Monitoring and surveillance of antibiotic resistance.

INDIVIDUAL PRECAUTIONS:-

- Frequent, thorough hand washing.
- Cleanliness when preparing and consuming food.
- Reinforcing precautions when in contact with persons with a urinary tract infection/diarrhea.

CONCLUSION

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It is difficult to treat patients infected by bacteria which harbor this new resistance mechanism, since NDM-1 is highly resistant to almost all antibiotics, including carbapenems. Currently, it appears that two antibiotics (tigecycline and colistin) are still effective, but resistance can occur. The severity of infections involving NDM-1 can vary from mild to fatal.The emergence and rapid dissemination worldwide of carbapenemresistance due to the NDM-1-encoding gene should be seriously monitored in order to avoid any risk of pandemia.In this study the demonstrate the good specificity of a real-time polymerase chain reaction (PCR) assay for the detection of this alarming gene on a large panel of clinically relevant bacteria that may share carbapenemresistance-encoding genes.

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PROCEEDING -33

LAWSONIA INERMIS (HEENA): PHARMACOGNOSTICAL, PHYTOCHEMICAL & PHARMACOLOGICAL REVIEW

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INTRODUCTION

Plants have played a significant role in maintaining human health & improving the quality of human life for thousands of years. Ethnopharmacological studies on such medicinally important plants continue to interact investigators throughout the world. One such plant, Heena (*Lawsonia inermis* L.) invites attention of the researchers worldwide for its pharmacological activities ranging from anti-inflammatory to anti-cancer activities. The word henna which means "to become queen'' is indicative of something highly elegant. This plant has been described in Charaka Samhita for the treatment of epilepsy and jaundice and for dyeing grey hairs. The different species of *Lawsonia inermis* L. are *Lawsonia alba* and *Lawsonia spinoza/spinosa*.

TAXONOMICAL CLASSIFICATION

Kingdom: Plantae
Divison: Angiospermae
Class: Dicotyledons
Order: Myrtalas
Family: Lythraceae
Genus: *Lawsone*
Species: *Inermis*

- **GEOGRAPHICAL DISTRIBUTION**

Heena is mainly distributed in Egypt, Arabic countries, Persian countries, India, Pakistan, USA(Florida), China and Sudan. *L.inerms* is a much branched shrub that grows in middle east of Africa is commonly known as Mehndi in Hindi, Mendika in Sanskrit, Mailanchi in Malayalam, Maruthani in Tamil, Benjati in Oriya, Mayilanchi in Kannada, and Mehedi in Bengali.

- **MORPHOLOGICAL CHARACTERS**

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The leaf of *L.inermis* is short, smooth, ovate lanceolate, acute, symmetrical, entire, pinnate, opposite, sweet smelling, characteristic or bitter in taste and varies in length. Lawsone is mainly present in the marginal vein or petiole in large quantities. *L.inermis* is characterised by the presence of distinct midrib from lamina which is broadly shallow on adaxial side and convex on abaxial side.The leaf of the plant is dorsiventral as oblong palisade cell are present below the upper epidermis and absent on lower epidermis.

- **PHYTOCHEMICAL REVIEW**

The principal colouring matter of heena is lawsone,2-hydroxyi1,4-napthaquinone ($C_{10}H_6O_3$,Melting point: 190°C). Besides lawsone, other constituent present in *L. inermis* are gallic acid, glucose, mannitol, fats, resin, mucilage and traces of an alkaloid. Leaves yield hennatonic acid and an olive oil green resin, soluble in ether and alcohol.

- **PHARMACOLOGICAL REVIEW**

The extensive survey of literature revealed that *L. inermis* L. is highly regarded as a universal panacea in the herbal medicine with diverse pharmacological activity spectrum. The plant has been reported to have analgesic, hypoglycemic, antimalarial, hepatoprotective, nootropic, immunostimulant, anti-inflammatory, antibacterial, antimicrobial, antifungal, antiviral, antiparasitic, antitrypanosomal, antidermatophytic, antioxidant, anthelmintic, antifertility, tuberculostatic and anticancer properties. It is now considered as a valuable source of unique natural products for development of medicines against various diseases and also for the development of industrial products.

- **CONCLUSION**

Henna, the potential medicinal plant is a unique source of various pharmacologically important compounds. This multifunctional ayurvedic herb may be explored further to develop novel therapeutically active drugs molecules. As the global scenario is now changing towards the use of safer non toxic plant products with ethno pharmacological use, development of modern drugs from henna should be emphasized for the control of various diseases. Henna imbibing a tremendous potential deserves a special attention of the scientific fraternity to emerge as a milestone for medical science of this millennium.

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PROCEEDING -34

Herbal Drugs Used For the Treatment of Cancer

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INTRODUCTION

Cancer is the uncontrolled growth of abnormal cells in the body. Cancerous cells are also called malignant cells. Cancer grows out of normal cells in the body. Normal cells multiply when the body needs them, and die when the body doesn't need them. Cancer appears to occur when the growth of cells in the body is out of control and cells divide too quickly. It can also occur when cells forget how to die. There are many different kinds of cancers. Cancer can develop in almost any organ or tissue, such as the lung, colon, breast, skin, bones, or nerve tissue.Various herbal drugs are available and well established for the treatment of cancer. They include periwinkle (*Catharanthus roseus*, Apocynaceae), Himalayan mayapple (*Podophyllum hexandrum,* Berberidaceae), talispatra (*Taxus brevifolia*, Taxaceae), camptotheca (*Camptotheca acuminate*, Nyssaceae),

guduchi (*Tinospora cardifolia,* Menispermaceae). Other herbs possessing anti cancerous activity include the following:

GREEN TEA

The leaves of *Camellia sinensis,* Thaeceae are referred to as green tea. Its anticancer activity is due to presence of high content of EGCG (epigallocatechin-3-gallate), which is believed to suppress breast cancer growth.

BLACK RASPBERRY

It consists of fruits of *Rubus occidentalis,* Rosaceae. It is used in treatment of oesophageal and colon cancer.

MANDUKPARNI

The drug consists of herb of *Centella asiatica,* Umbelliferae. Its antineoplastic activity is thought to be due to the presence of flavanoids. It is at times used for treatment of brain cancer. One of its marketed brands includes Himalaya Mandukparni.

GARLIC

The bulbs of garlic i.e. *Alliun sativum*, Liliaceae contains a mixture of E- and Z-isomers (E- and Z-4,5,9-trithiadodeca-1,6,11-triene 9-oxide) which on being heated in presence of moisture forms Ajoene that has antitumour properties. It is used in case of stomach cancer.

TULSI

The leaves of *Ocimum sanctum,* Labiateae contain urosolic acid and oleanlic acid that possesses anticancer properties is used in lung cancer.

CURCUMIN

Curcumin is from the turmeric herb, *Curcuma longa,* Zingiberaceae and is another herb that is better known as a spice than as an anti-cancer treatment.

SAFFRON

Saffron, *Crocus sativus,* Iridaceae is probably better known as a spice than as a medicinal herb, but it has been found to have anti-cancer properties. When applied topically, saffron is able to help prevent the development of skin cancers.

ALOE VERA

Aloe vera is a controversial treatment for inhibiting cancer growth. It is the gel of the aloe that contains the nutrients that appear to have anti cancer and cancer fighting properties.

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PROCEEDING -35

NOVEL ANTICANCER AGENTS FROM HERBS

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INTRODUCTION**:**

Cancer is a term that is used to refer a number of conditions where the body cells begin to grow and reproduce in an uncontrollable way. This rapid growth of cancerous cells is known as a malignant tumor. These cells can then invade and destroy healthy tissue, including organs. Cancer sometimes begins in one part of the body before spreading to other parts. This process is known as metastasis. Cancer is a serious health problem across the world. It is estimated that 7.6 million people in the world died of cancer in 2007[1,2].

HERBAL MEDICINE IN CANCER TREATMENT: Herbal medicines have a vital role in the prevention and treatment of cancer. Countries like USA, Germany, France, Japan and China, considerably improved the quality

of the herbal medicines used in the treatment of cancer. The therapeutic effect of anticancer herbs is executed by inhibiting cancer-activating enzymes, stimulating DNA repair mechanism, promoting production of protective enzymes, antioxidant action and by enhancing activity of the immune cells.

PLANTS HAVING ANTICANCER ACTIVITY:

1. *Catharanthus roseus* or *Vinca rosea* (Periwinkle) contains vinca alkaloids, vinblastine and vincristine which were the first phytoconstituents ever used to treat cancer. Vinca alkaloids execute anticancer effect by binding to the tubulin, thus inhibiting formation of mitotic spindle in the metaphase that arrests division of the cancerous cells. Vinblastine is used in the treatment of Hodgkin's, non-Hodgkin's lymphoma and cancers of the kidney and testis[3].

2. *Podophyllum peltatum* (American May Apple) and ***Podophyllum hexandrum*** (Himalayan May Apple) contain podophyllotoxin which arrests multiplication of cancerous cells by breaking down the microtubules into smaller subunits, thus inhibiting the cell division. It is used in the treatment of Hodgkin's disease, non-Hodgkin's lymphoma, leukaemia, bronchogenic carcinoma and cancers of ovary and testis[4].

3. *Taxus brevifolia* (Pacific Yew Tree), ***Taxus yunnanensis*** (Yunnan Yew Tree) and ***Taxus baccata*** (European Yew Tree) contain taxanes; paclitaxel (Taxol) and docetaxel (Taxotere) which arrest multiplication of cancerous cells by cross-linking the microtubules. Taxanes are used to treat leukaemia and cancers of breast, ovary, colon and lung[5].

4. *Camptotheca acuminata* and ***Mappia foetida*** contain camptothecin, a quinoline alkaloid which inhibits topoisomerase-I enzyme. Derivatives of camptothecin; topotecan and irinotecan have been found to possess strong antileukaemic activity[6].

5. *Allium sativum* (Garlic) contains diallyltrisulphide, diallyldisulphide and S-allyl-cysteine having anticarcinogenic properties. Garlic extract protects DNA from the damaging effect of carcinogens, increases activity of detoxifying enzymes, speeds up excretion of chemical carcinogens and enhances immunity of the body[7].

6. *Aloe vera* (Ghrit kumari) contains aloe-emodin, which activates the macrophages to fight against cancer. It also contains acemannan, which enhances activity of the immune cells. Aloe vera extract is found to inhibit metastases[7].

7. *Combretum caffrum* (African Willow Tree) contains combretastatin, which has been isolated recently. Combretastatin executes its therapeutic action against cancer by inhibiting blood supply to the tumour[7].

8. *Camellia sinensis* (Green tea) contains epigallocatechin gallate, which prevents covalent bonding of carcinogens to the DNA and eliminates free radicals from the body. It also protects the body from damaging effects of radiation[8].

9. *Curcuma longa* (Turmeric) contains curcumin, which inhibits the growth of cancer by preventing production of harmful eicosanoid such as PGE-2. Curcumin shows anticancer effect in all steps of cancer development. It suppresses mutagenic effect of various mutagens and also possesses anti-inflammatory and antioxidant properties[9].

10. *Ginkgo biloba* (Yin Guo) contains Ginkgolide-B, which inhibits growth of cancer by regulating activity of the platelet-activating factor and protects the DNA from damaging effects of nuclear radiation[10].

Bioflavonoids are the water-soluble pigments found in vegetables and fruits include citrin, hesperidin, rutin, quercitin, epicatechin, flavones, flavonols, proanthocyanins and anthocyanins. They possess antioxidant properties and inhibit growth of cancerous cells by scavenging free radicals. Other important anticancer herbs includes *Benincasa hispida, Brassica oleracea, Calendula officinalis, Dirca occidentalis, Feddiea fischeri, Larrea divaricata, Larrea tridentata, Morus alba, Ostodes paniculata, Passerina vulgaris, Piper futokadsura, Soulamea soulameoides, Trichosanthes kirilowii* and *Urtica dioica*[11,12].

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CONCLUSION: Increased adverse affect by chemotherapy with common drugs like alkylating agents, antimetabolites, antibiotics and steroid analogues offer the treatment system return to nature. Herbal drugs such as vincristine, vinblastine, taxols and etoposide show lesser toxicity and better effectiveness in numbers of oncological conditions. Scientists are focusing on the herbal medicines to understand the complex synergistic interactions and to design herbal formulations with minimum adverse affects.

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PROCEEDING -36

MOLECULAR SIMULATION - KEY TO DESIGNING NEW DRUGS

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INTRODUCTION

A tool for predicting entirely computationally many useful functional properties of systems of interest in the chemical, pharmaceutical, materials, and related industries. Included are thermodynamic, thermochemical, spectroscopic, mechanical, and transport properties, and morphological information (such as location and shape of binding sites on a biomolecule and crystal structure). The two main molecular simulation techniques are molecular dynamics and Monte Carlo simulation, both of which are rooted in classical statistical mechanics. Given mathematical models for the internal structure of each molecule (the intramolecular potential which describes the energy of each conformation of the molecule) and the interaction between molecules (the intermolecular potential which describes the energy associated with molecules being in a particular conformation relative to each other), classical statistical mechanics provides a formalism for predicting properties of a macroscopic collection of such molecules based on statistically averaging over the possible microscopic states of the system as it evolves under the rules of classical mechanics. Thus, the building blocks are molecules, the dynamics are described by classical mechanics, and the key concept is statistical averaging.

International Journal of Pharma and Bio Sciences
ISSN 0975 - 6299

In molecular dynamics, the microscopic states of the system are generated by solving the classical equations of motion as a function of time (typically over a period limited to tens of nanoseconds). Thus, one can observe the relaxation of a system to equilibrium (provided the time for the relaxation falls within the time accessible to molecular dynamics simulation), and so molecular dynamics permits the calculation of transport properties which at the macroscopic scale describe the relaxation of a system in response to inhomogeneities. In Monte Carlo simulation, equilibrium configurations of systems are generated stochastically according to the probabilities rigorously known from classical statistical mechanics. Thus, Monte Carlo simulation generates equilibrium states directly (which has many advantages, including bypassing configurations which are not characteristic of equilibrium but which may be difficult to escape dynamically) and so can be used to study equilibrium configurations of systems which may be expensive or impossible to access via molecular dynamics. The drawback of Monte Carlo simulation is that it cannot yield the kind of dynamical response information that leads directly to transport properties. Computational quantum chemistry and molecular simulation methods can be used to predict properties that once were only accessible experimentally, resulting in several significant applications in basic and industrial research. These applications include providing estimates of properties for systems for which little or no experimental data are available, which is especially useful in the early stages of chemical process design; yielding insight into the molecular basis for the behavior of particular systems, which is very useful in developing engineering correlations, design rules, or quantitative structure-property relations; and providing guidance for experimental studies by identifying the interesting systems or properties to be measured. The binding process of a drug, to its target protein is highly dynamic and depends on interactions at a nanometric scale and occurs at timescales of nano/micro-seconds. The method provides not only the binding affinity and the kinetics of the reaction, but also information about the atomic resolution during the process: transition states and metastable states are potentially useful for expanding the probability of success when designing drugs. The researchers are working to expand the applicability of this methodology, in cases where ligands are larger and more flexible. Current limitations of molecular simulation techniques are the molecular simulation algorithm and computation time for complex systems. Force field algorithms are currently quite efficient and are often used today. However, such models neglect electronic properties of the system. In order to calculate electron density, quantum mechanical models are required. However, as the number of atoms and electrons is increased, the computational complexity of the model quickly reaches the limits of our most modern supercomputers. Molecular simulation is able to provide and predict data about molecular systems that would normally require enormous effort to obtain physically. By organizing virtual atoms in a molecular simulation environment, one can effectively model nanoscale systems

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PROCEEDING -37

Pyrimidine: The molecule of immense interest

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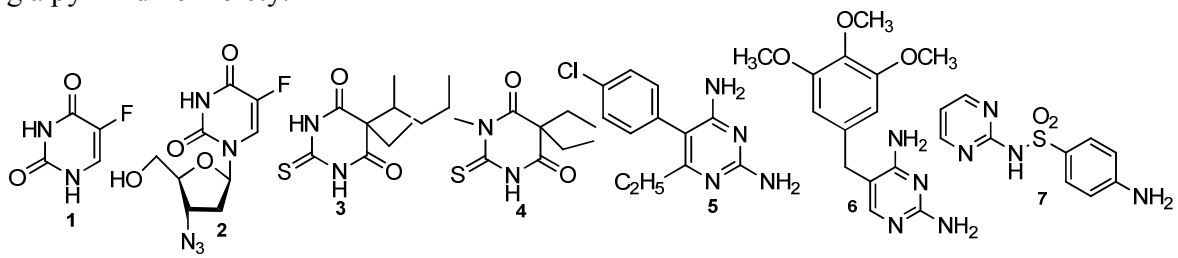
INTRODUCTION

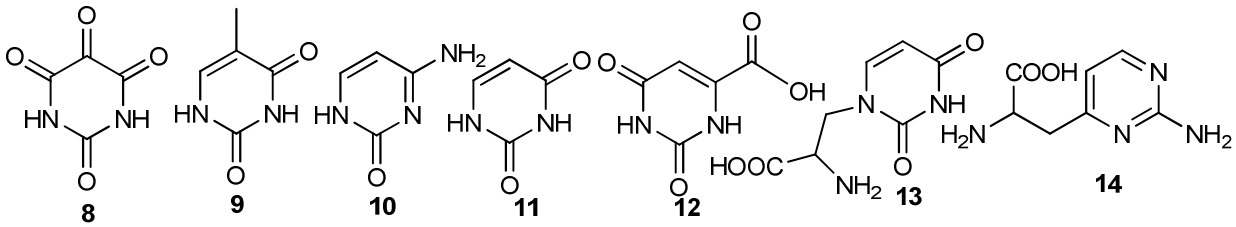
Over the year the pyrimidine system turned out to be an important pharmacophore, interacting with the synthesis and function of nucleic acids viz. cytostaticum fluorouracil (**1**) or the HIV drug zidovudine (**2**)

Ultrashort-acting barbiturates such as thiopental sodium (**3**) are often used as general anaesthetic, whereas methylphenobarbitone (**5**) still is in use as antiepilepticum. Some diaminopyrimidines like pyrimethamine (**6**) or trimethoprim (**7**) are powerful antimalarial drugs. Sulphadiazine is one of the most chemotherapeutics containing a pyrimidine moiety.



NATURAL COMPOUNDS HAVING PYRIMIDINE NUCLEUS

The first pyrimidine derivative, (alloxan,**8** to be isolated was obtained in 1818 by *Brugnatelli*, oxidising uric acid with HNO_3. Thymine (**9**) was isolated from hydrolyzates of bovine thymus or spleen in 1893. Cytosine (**10**) was isolated from hydrolysis of calf thymus. Uracil (**11**) was first isolated from the hydrolysis of herring sperm in 1900. In 1905 orotic acid (**12**) was isolated from the whey of cow's milk. In 1959, a non-proteinogenic L-α-amino acid, Willradine (**13**) was isolated from the seeds of *Acacia willaradiana.* The extracts of *L. tinigitus* appeared to contain the highest concentration of tingitanine. (**14**) Vitamine B_1 (aneurine, thymine), the antineuritic or anti-beriberi vitamine, a water soluble substances belong to the vitamin B complex. It was first isolated form rice bran by Jansen and Donath in 1926. The simplest pyrimidine antibiotic is bacimethricin, a naturally occurring thiamine antimetabolite, which was isolated from *Bacillus megatherium.*



ANTICANCER COMPOUNDS HAVING PYRIMIDINE NUCLEUS

Gavilan M. D. *et al.* reported the synthesis and anticancer activity of 1, 3, 5- tetrahydro-4, 1-benzoxazepine-3-yl-pyrimidines (**15**) (IC50 =1.25-6.75µM on MCF-7cell). Ahmed O.M, *et al.* have studied the synthesis and antitumor cytotoxicity of Pyrazolo [1, 5-a] pyrimidine derivative (**16**).Gangjee A. *et al* reported the synthesis of N^4-phenyl substituted-6-(2,4-dichlorophenyl methyl)-7H-Pyrrolo[2,3-d] pyrimidine-2,4-diamines (**17**) and evaluated for in-vivo anticancer activity against the B16-F10 (lung clononizing) melanoma implanted in arrthymic male mice.

ANTICONVULSANT COMPOUNDS HAVING PYRIMIDINE NUCLEUS

A number of *N*-(4,6-substituted diphenylpyrimidin-2-yl) semicarbazones were synthesized and tested for their anticonvulsant activity. A series of N0-[substituted] pyridine-4-carbohydrazides (**18**) were also designed and synthesized keeping in view the structural requirement of pharmacophore and evaluated for anticonvulsant activity and neurotoxicity. The most active compound of the series was N-[4-(4-fluorophenoxy)benzylidene]pyridine-4-carbohydrazide PCH 6, which showed a MES ED_{50} value of 128.3 mg/kg and 6 Hz ED_{50} value of 53.3 mg/kg in mice.

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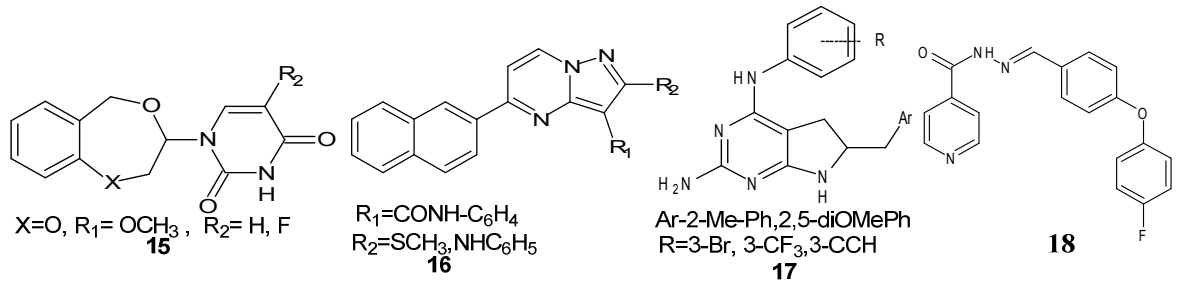
ISSN 0975 - 6299



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PROCEEDING -38

ANTI-COAGULANT/ANTI-THROMBOTIC ACTIVITY OF NATURAL MEDICINAL PLANTS

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INTRODUCTION

Thromboembolic disorders such as pulmonary emboli, deep vein thrombosis, strokes and heart attacks are the main causes of morbidity and mortality in developed countries.[1]Coagulation is a defence function of the organism that has to be strictly regulated. Antithrombotic agents are widely used for treating haemostatic impairments such as coronary angioplasts, coronary thromboembolism, myocardial heart attack, pulmonary embolism.[2] During the past five decades, anticoagulant therapy has consisted of rapidly acting parenteral drugs (unfractionated heparin{UFH}low molecular weight heparins{LMWH})for prevention of venous thromboembolism and initial treatment of arterial and venous thromboembolism, whereas Vitamin K antagonists (VKA) are used for long term oral treatment.

Plants have been used as alternative sources for the development of new anticoagulant agents due to their biological activities and specially the extracts which provide a useful source of bioactive compounds which can be developed as drugs directly or provide novel structural templates.[3]

ANTICOAGULANT/ANTITHROMBOTIC ACTIVITY OF NATURAL PLANTS

Plant name	Plant part & type of extract	Chemical constituents	Anticoagulant/Antithrombotic activity
Careya arborea Roxb. (kumbhi) Fam. Lecythidaceae	Bark (Methanolic extract)	Terpenoids, flavonoids, alkaloids, Saponins & tannins[4]	Methanolic bark extract prolonged the blood clotting time with an increase($p<0.05$) in activated Partial Thromboplastin Time,Prothrombin time and Thrombin time when compared with standard warfarin[5]

Melastomamalabathricum Linn. Fam.Melastomataceae	Leaves(Aqueous extract)	Amides,triterpenoids,flavonoids, Alkaloids & tannins[6]	In vitro results show Aptt of plasma samples spiked with different concentrations of leaf extract markedly prolonged in a concentration dependent manner($p<0.001$).[7]
Gloriosasuperba Linn.(glory lily) Fam.Liliaceae	Leaves(Different extracts)	Gloriosine & Colchicines	Inhibition of thrombin induced clotting,with IC value of 2.97mg/ml.[8]
Bauhiniaforficata (Pata De Vaca) Fam.Leguminosae	Aerial parts(Aqueous extract)	Flavonols,flavonoids,glycosides, Kaempferitrin,astragalin,β-sitosterol, quercitrosides,	Source of natural inhibitors of serine protease involved in blood clotting disturbances induced by snake venoms.[9]
Eichhorniacrassipes (Common water hyacinth) Fam.Pontederiaceae	Leaf(Methanolic extract)	Tannins,flavonoids,alkaloids, Terpenoids, glycosides[10]	Acts on the intrinsic pathway of the coagulation cascade.[11]
Jatrophacurcas Linn. Fam.Euphorbiaceae	Latex		Whole latex reduced ($p<0.01$) clotting time of human blood.
Synclisiascabrida(Meris) Fam. Menispermaceae	Whole shrub (Aqueous & ethanolic extract)		Significantly prolonged ($p<0.05$)the Prothrombin time of normal plasma[12]
Poranavolubilis(Horse tail creeper) Fam. Convolvulaceae		Galactose,mannose & galacturonic acid	Enhancement of thrombin inhibition in turn mediated by heparin cofactor ll.[13]
Viola yedoensis Makino		Dimeresculetin(dicoumarin)	Exhibits the activity with respect to activated Partial Thromboplastin Time, Prothrombin Time & Thrombin Time[14]

CONCLUSION

With the advent of allopathic system of medicine which is based on the fast therapeutic actions has gradually lost its popularity among people .But traditional medicines have been used to alleviate the suffering of human beings.Despite the widespread usage of traditional medicines, they have not been evaluated scientifically with regard to their safety and efficacy and has many limitations[15].Various herbal drugs mentioned in different traditional systems of medicine across the world require more exploitation upto desired level, and this report could be a better target for the development of alternatives to synthetic anticoagulant drugs.

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PROCEEDING -39

Emerging Challenges in New Drug Discovery

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INTRODUCTION:

New Drug discovery isa complex and demanding area in the field of pharmaceutical research. In recent years there are been increasing awareness about the importance ofpredicting/optimizing the absorption, distribution, metabolism, excretion and toxicity (ADMET)properties of small chemical compounds along the search process rather than at the final stages.ADMET problems associated with drug candidates are the most important reasons for increased cost of drugs.ADMET prediction and its assessment is still a major challenge for the medicinal chemist and a major hurdle in the field of new drug discovery.Thus it is necessary that the Fast methods for

evaluating ADMET properties of small molecules often involve applying a set of simple empirical rules (educated guesses) and as such, compound collections' property profiling canbe performed in-silico. Clearly, these rules cannot assess the full complexity of the human body butcan provide valuable information and assist decision-making[1].

ADMET PREDICTION TOOLS:

Various tools are available for prediction of absorption, distribution, metabolism, excretion and toxicity properties of drug candidates. The software for calculating ADMET properties are summarized in **Table 1**.

Table 1

Software for calculating ADMET properties

Programs	**Parameters prediction**
Biobyte ClogP[1-2] or ACD LogP v4.0	Oral bioavailability
tPSA[4]	Oral bioavailability
PALLAS MetabolExpert	PredictingpKa,logP, logD values and Metabolites
Quanta 3D	Blood-brainbarrier penetration and membrane permeability
BiobyteClogP v4.3	Toxicity
BiobyteClogP	Toxicity
ADMET prediction	ADMET properties
Molinspiration	logP, molecular polar surface area, molecular weight, molecular volume, number of rotatable bonds and bioactivity
Osiris calculator	Tumorogenicity, mutagenicity, irritation, reproduction effectivity,clogP, solubility, drug-likeness and drug score

SUMMARY:

Modeling the ADMET properties during the early stage of drug discovery has become the necessary task to perform. Various in-silico ADMET prediction tools are available which can be used in primary stages of drug development. In summary it can be stated that the ADMET issues need to be estimated carefully in order to reduce the cost of drug discovery and facilitating the process of finding the new drugs.

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ISSN 0975 - 6299

MULTIDIMENSIONAL QSAR: PREDICTION BEYOND THE THIRD DIMENSION

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INTRODUCTION

Drug design is a process driven by innovation and technological breakthroughs involving a combination of advanced experimental and computational methods. A broad variety of medicinal chemistry approaches can be used for the identification of hits, generation of leads, as well as to accelerate the optimization of leads into drug candidates. The quantitative structure–activity relationship (QSAR) formalisms are among the most important strategies that can be applied for the successful design new molecules. The identification of promising hits and the generation of high quality leads are crucial steps in the early stages of drug discovery process. Drug discovery is currently driven by innovation and knowledge employing a combination of experimental and computational methods. Quantitative structure-activity relationships (QSAR) play a vital role in modern drug design, since they represent a much cheaper and rapid alternative to the medium throughput in vitro and low throughput in vivo assays which are generally restricted to later in the discovery cascade.

Quantitative structure-activity relationship (QSAR) is based on the general principle of medicinal chemistry that the biological activity of a ligand or compound is related to its molecular structure or properties, and structurally similar molecules may have similar biological activities. Such molecular structural information is encoded in molecular descriptors and a QSAR model defines mathematical relationships between descriptors and biological activities of known ligands to predict unknown ligands' activities. QSAR methods have been applied in several scientific studies including chemistry, biology, toxicology and drug discovery to predict and classify biological activities of virtual or newly-synthesized compounds. In other words, QSAR studies can reduce the costly failures of drug candidates by identifying the most promising hit compounds and reducing the number of costly experiments.

A wide range of QSAR methodologies have been invented traditional 2D-QSAR methods such as Free-Wilson and Hansch-Fujita models use 2D molecular substituents or fragments and their physicochemical properties to perform quantitative predictions. Since then, QSAR has experienced a fast development and the first novel 3D-QSAR method called comparative molecular field analysis (CoMFA) was introduced. The CoMFA method brought a foundation for the development of other 3D-QSAR methods such as CoMSIA, SOMFA, CoMMA as well as multidimensional (nD)-QSAR methods such as 4D-QSAR, 5D-QSAR, *etc*., to tackle known 3D-QSAR problems such as subjective molecular alignment and bioactive conformation problems.

Multi-Dimensional (nD) QSAR Methods

Multi-dimensional (nD) QSAR methods are essentially extensions of 3D-QSAR methods. These methods incorporate additional physical characteristics or properties (or a new dimension) to tackle the drawbacks of 3D-QSAR methods. One example is 4D-QSAR by Hopfinger *et al.* which samples molecular conformations and alignments during the generation of a QSAR model. While incorporating some CoMFA features, it introduces the fourth dimension, which is the conformational Boltzmann sampling, and enables the method to be used as a receptor-independent (RI) method as well as receptor-dependent (RD) method in which the geometry of the receptor is known. It should be noted that their 4D-QSAR method does not solve the alignment problem but it allows a rapid evaluation of individual trial alignments. Recently, it has been shown that 5D- and 6D-QSAR can be used for multiple representations of the receptor as well as its solvation states. 5D-QSAR method introduced a multiple representation of induced-fit hypotheses, *i.e.*, the adaptation of the receptor binding pocket to the individual ligand topology, as the fifth dimension. The binding affinities of new molecules

were predicted more accurately with 5D-QSAR than with other lower dimension models. In the reported 6D-QSAR model, the simultaneous consideration of different solvation models was introduced by mapping parts of the surface area with different solvent properties. 3D, 4D, 5D and 6D models were explored as comparison studies and the results showed the 6D-QSAR model produced the best predictive results.Hence QSAR models can also be used in designing new chemical entities (NCEs) and are now regarded as essential tools in pharmaceutical industries to identify promising hits and generate high quality leads in the early stages of drug discovery .

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PROCEEDING -41

URSOLIC ACID-A MULTIDIMENSIONAL APPROACH

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INTRODUCTION

Ursolic acid, also known as urson, prunol, micromerol and malol, is a natural pentayclic triterpenoid carboxylic acid compound which naturally occurs in a large number of vegetarian foods, medicinal herbs and other plants. For a long time, it was considered to be pharmacologically inactive. Contemporary scientific research which led to the isolation and identification of ursolic acid revealed and confirmed that several pharmacological effects like anti-tumor, hepatoprotective, anti-inflammatory (oral and topical), anti-ulcer, antimicrobial, anti-hyperlipidemic and antiviral, can be attributed to ursolic acid. However, its anti-inflammatory (topical), anti-tumor (skin cancer), and antimicrobial properties are pertinent to the cosmetics industry.

SOURCES OF URSOLIC ACID

1.**DIETARY SOURCES-** Apples, bilberries, cranberries, elder flower, peppermint, lavender, oregano, thyme, sage, hawthorn and prunes.

2.**OTHERS-**TULSI (*OCIMUM SANCTUM*), PERIWINKLE (*VINCA MAJOR*), NONI(*MORINDA CITRIFOLIA*) ROSEMARY (*ROSMARINUS OFFICINalis*).

THERAPEUTIC USES

1.AS A COSMECeutical- In cosmetics, ursolic acid has a variety of applications in skin & hair beautification and protection. It acts as stimulant for hair growth by stimulating the peripheral blood flow in the scalp and activating the hair mother cells, fights against dandruff and also treats other scalp problems. It creates a barrier on the skin that repels oil. It is used to treat photoaged skin because it prevents and improves the appearance of wrinkles & age spots by restoring the skin's collagen bundle structures & its elasticity. The use of ursolic acid on the skin can create more moisturized, younger-looking and feeling skin.

2.AS A PHARMACEUTICAL- Ursolic acid has medicinally action, both topically and internally. It has antimicrobial, antibacterial, antiviral and antifungal activity. Tests have shown that Ursolic acid inhibits the growth of *Candida albicans* and *Microsporium lenosum*. This also have potent anti-inflammatory property and

is used in ointments to treat burns. Topical application of ursolic acid inhibited TPA-induced initiation and promotion of tumor growth.

3.AS A NUTRACEUTICAL- Ursolic acid is used as food additive for its antioxidant effect & to prevent dental caries.

TOXICITY-Ursolic acid has an exceptionally low toxicity. This dermatological harmlessness makes it extremely valuable, as it can be used in a large number of products. It is proven safe for both external and internal use as well.

FORMULATIONS DEVELOPED- Phytosomes, Ethosomes, Anti-inflammatory cream, Extended release tablets, Capsules, Liposomes, Phospholipid nanoparticles, Merospheres.

FUTURE PROSPECTS

Ursolic acid is a dynamite in the world of herbal compounds with a great potential. Ursolic acid can also serve as a starting material for synthesis of more potent bioactive derivatives, such as anti-tumor agents. A lot of research work is going on & has to be done for ursolic acid alone as well as in combination therapy. In coming future, it will prove a boon for pharma professional & common man too.

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PROCEEDING -42

SELF MEDICATION: A CHALLENGE FOR DRUG DISCOVERY AND DEVELOPMENT

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INTRODUCTION

Medication refers to the act of consuming medicines for prevention, diagnosis or treatment of diseases. Correct medication is observed by reporting any symptom or disease to the physician in the hospital or clinic who diagnoses and prescribes the needed drugs to alleviate the condition. This is usually followed by filling of such prescriptions at the pharmacy by the pharmacist. [1] While Self-medication, is the selection and use of medicines by individuals to treat self-recognized illnesses or symptoms. The medicines of self-medication are called as "over the counter" (OTC) medicines and are available without a doctor's prescription.[2]

CAUSES OF SELF MEDICATION

Self medication is a fairly common practice, especially in developing countries where professional health care is relatively expensive and in some cases not readily available thereby making self medication an obvious choice of healthcare service.[3] Self medication may also generate substantial net benefit flows to economies through saving in travel and consultation time and the direct financial cost of treatment.[4] There are several other various causes of self medication also which is described in fig 1.

International Journal of Pharma and Bio Sciences
ISSN 0975 - 6299

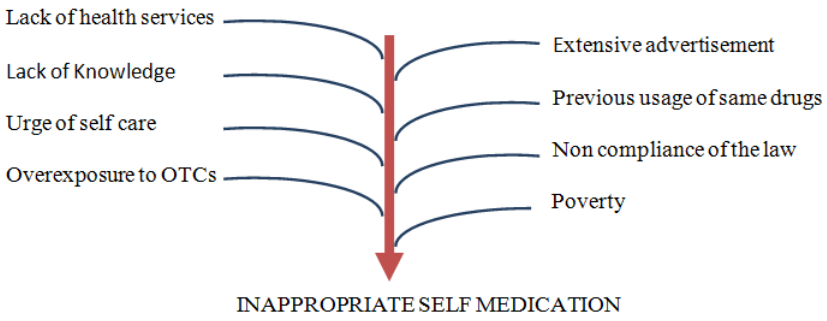

Figure 1
. *Various causes of self medication*

HARMFUL EFFECTS OF SELF MEDICATION

Due to self exposure of drugs without proper medication it leads to various adverse effects like skin problem, hypersensitivity, toxic effects, allergy, poisonings, habituation, addiction, development of the resistance to the drugs and sometimes due to wrong medication it may even lead to death also. Moreover, their uses often delays proper treatment of the diseases.[5] Various effects of self medication is shown in fig 2.

COMMON DRUGS USED FOR SELF MEDICATION

People generally don't prefer to consult the doctor for the minor ailments like headache, cough, cold, sore throat, stomach ache, fever, vomiting, diarrhea etc and thereby believe in self care.[6] Common drugs which are used for self medication is as shown in table 1

SEVERAL WAYS TO OVERCOME SELF MEDICATION

By seeing the various adverse effects of self medication it is very much necessary to control and to take various preventative measures for the betterment of an individual and society.[7, 8]

Various steps should be followed to overcome self medication: [9]

- Strict compliance of the law regarding sale and advertisement of the drugs.
- Awareness should be created in the community by educating the various risk factors associated with the indiscriminate use of the potent drug molecules.
- A proper statutory drug control for the availability of drugs to the public for over the counter (OTC) drugs must be implemented as well.
- Governments and health authorities should become strict about the rules and need to ensure that it is done in a responsible manner.
- Individual should have full knowledge about the drugs and disease and if not they should consult the physician for proper medication.

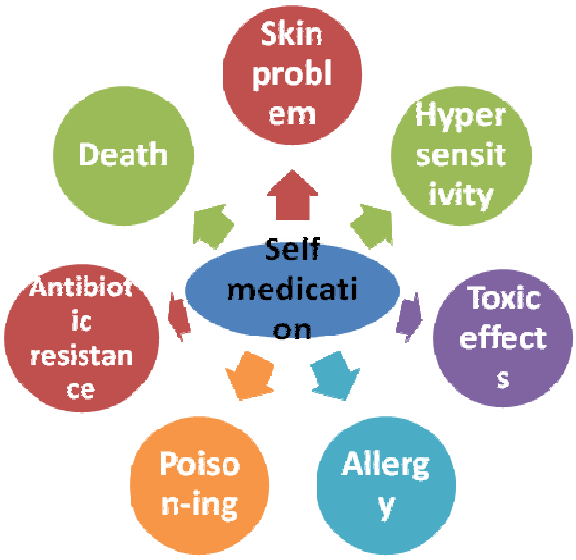

Figure 2.
Harmful effects of self medication

Table 1
Common drugs used for self medication

Sr. no	Category	Drugs used for self medication
1	Antitussives	D-cold total, Corex, Vicks Action 500, Benadryl, Glycodin, Cetrizen, Honitus, Avil etc
2	Antibiotics	Ciprofloxacin, Norfloxacin, Amoxicillin, cefadroxil etc
3	Antiseptics	Dettol, Savlon, Soframycin, Boroplus etc
4	Antipyretics	Paracetamol, Ibuprofen, Calpol, Crocin etc
5	Analgesics	Saridon, Disprin, Nise, Diclofenac, Nimesulide etc
6	Antidepressant	Nicotine, alcohol, tea, coffee etc
7	Miscellaneous	Dabur chyawanprash, Hajmola, steroids etc

CONCLUSION

By seeing the current scenario of usage of over the counter drugs it is concluded that the number of individual enrolled in self care is much higher and it causes various side effects and ultimately lead to an unhealthy society, Though there are number of advances in drug discovery for curing disease but the major monster amongst all is the prevalence of self medication amongst an individual which should be completed eradicated for creating a healthy society. Hence, various preventative measures should be taken by the government by creating awareness, by educating the various risk factors associated with it and by following strict compliance of the law. These measures would definitely reduce the incidence of drug-related mishaps and help in maintaining good health of the individual and society.

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PROCEEDING -43

ANTIMICROBIAL RESISTANCE: A MEDICAL CONCERN

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INTRODUCTION

Antimicrobial resistance (AMR) is resistance of a microorganism to an antimicrobial medicine to which it was previously sensitive. Resistant organisms (they include bacteria, viruses and some parasites) are able to withstand attack by antimicrobial medicines, such as antibiotics and antivirals, so that standard treatments become ineffective and infections persist and may spread to others. AMR is a consequence of the use, particularly the misuse, of antimicrobial medicines and develops when a microorganism mutates or acquires a resistance gene.

Antibiotic-resistant pathogens are not more virulent than susceptible ones: the same numbers of resistant and susceptible bacterial cells are required to produce disease, but the resistant forms are harder to destroy.

If a bacterium carries several resistance genes, it is called multiresistant or, informally, a superbug or super bacterium.Few of the many bacteria resistant to antimicrobials include MRSA (methicillin-resistant *Staphylococcus aureus*), *Streptococcus pneumoniae* (resistant to penicillin and other beta-lactams), *Mycobacterium tuberculosis* (resistant to isoniazid and rifampin). Multidrug resistant organisms include Vancomycin Resistant Enterococci (VRE), MRSA, Extende Spectrum ß-lactamse (ESBLs) producing gram-negative bacteria, *Klebsiella pneumoniae* carbapenemase (KPC) producing gram-negatives, Imipenem resistant or MultiDrug Resistant Organisms.

FACTORS ASSOCIATED WITH THE SPREAD OF ANTIMICROBIAL RESISTANCE

❖ Inappropriate use of antibiotics which includes-

- worldwide over use of antibiotic.
- incomplete or incorrect therapeutic regimens.
- availability of antibiotics without prescriptions.

❖ Prevalence of resistant genes.
❖ Failure of hospital infection control policies.
❖ Long-term exposure to low doses of antibiotics in animals as a "growth enhancer "and for preventing bacterial infections.
❖ Lingering antibiotic residues used in agriculture for preventing bacterial infections.
❖ Household use of antibacterials in soaps and other products, also contributes to resistance.

RESISTANCE MECHANISM

Bacteria owe their drug insensitivity to resistance genes.

➢ These genes might give rise to enzymes (such as lactamases) that degrade the antimicro-bial agents before it can show its effect.
➢ Such genes might code for "efflux" pumps that eject antibiotics from cells before it reaches the target site.(tetracyclines,macrolides)
➢ Some resistance genes cause bacteria to alter or replace molecules that are normally bound by an antibiotic.(vancomycin,methicillin)
➢ Some genes chemically alter—and inactivate—the drugs.

RESISTANCE GENES CAN BE ACQUIRED IN THE FOLLOWING WAYS:

- From their forerunners.
- Through mutations.
- By taking up resistance genes from other bacterial cells in the vicinity-horizontal gene transfer.
- A virus may pick up a resistance gene from one bacterium and inject it into a different bacterial cell.

CONSEQUENCES OF ANTIMICROBIAL RESISTANCE

▪ Bacterial resistance often results in treatment failure, which can have serious consequences, especially in critically ill patients.
▪ Prolonged therapy with antimicrobial agents, such as vancomycin or linezolid, may also lead to the development of low-level resistance that may not be detected by routine susceptibility testing methods used in hospital laboratories.
▪ Resistant bacteria may also spread and become broader infection-control problems, not only within healthcare institutions, but in communities as well.
▪ The spread of resistant bacteria within the community poses obvious additional problems for infection control; antibacterial drug resistance places an added burden on healthcare costs.
▪ It causes an increase in the number and duration of hospitalization.
▪ It is responsible for increased morbidity and mortality.
▪ Emergence of strains totally resistant to all available antimicrobials
▪ Choice of more expensive or more toxic therapeutic alternatives.

CONTROL OF THE SPREAD OF ANTIMICROBIAL RESISTANCE

o Restrict use of antibiotics for inappropriate indications.
o Eliminate the use of antimicrobials in animal husbandry and agriculture.
o Antibiotic restriction in hospital settings.
o Enforce infection control policies.
o Prescription of antibiotics that target only a narrow range of bacteria.
o Completing the full course of treatment exactly as prescribed.

International Journal of Pharma and Bio Sciences
ISSN 0975 - 6299

o Avoiding use of soaps and other products with antibacterial chemicals.

ANTIMICROBIAL RESISTANCE IN INDIA: NDM-1

New Delhi metallo-beta-lactamase-1 was first detected in a *Klebsiella pneumoniae* isolate from a Swedish patient who fell ill with an antibiotic-resistant bacterial infection that was acquired in India; and hence the name.

NDM-1 is an enzyme that makes bacteria resistant to a broad range of beta-lactam antibiotics, these include the antibiotics of the carbapenem family .The gene for NDM-1 is one member of a large gene family that encodes beta-lactamase enzymes called carbapenemases.

PROCEEDING -44

Potentials and future prospects of Cucurbitacins as medicinal leads

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INTRODUCTION

The cucurbitacins are a group of highly oxygenated triterpenoids possessing a 19(10→9β)-abeo-10α-lanost-5-ene skeleton (including a gem-dimethyl group at C-4 and further methyls at C-9 and C-14). The first cucurbitacin was isolated as a crystalline substance in 1831 and was named α-elaterin. Medicinal and toxic properties of these compounds have stimulated a continuing interest in them. Cucurbitacins with rich variety of side chain derivatives possess different pharmacological activities. The chemical structures of seventeen cucurbitacins are known and are identified by letters: A, B, C, D, E, F, G, H, I, J, K, L, O, P, Q, R and S. The term "cucurbitacin" refers to any form of cucurbitacin, including those forms listed above, or to the glycosides of any of these forms [1]. Cucurbitacins are usually reported as cytotoxic compounds, but there are clear differences between the toxicity and activity of cucurbitacins, depending on the pattern of substitution. Cucurbitacins D & I which are among the most toxic cucurbitacins have been reported to possess unsaturated side chain (Δ_{23}) and free hydroxyl group at C_{25}. Although instances of poisoning have been reported after consumption of cucurbitaceous food products, only few studies on the in- vivo toxicity of cucurbitacins have been described [2].

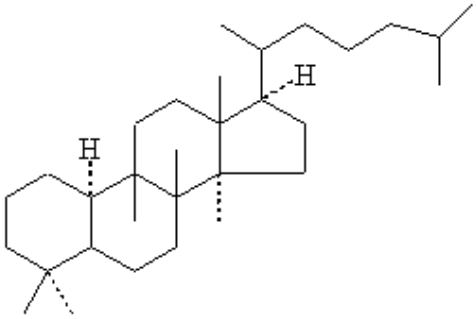

Figure. 1
Cucurbitacin skeleton

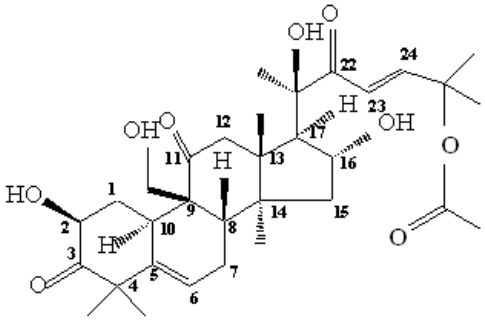

Figure. 2
Numbered heterocyclic nucleus of Cucurbitacin Analogue (cucurbitacin A)

PHARMACOLOGICAL POTENTIALS

The pharmacological potentials of various cucurbitacin analogues have been summarized in table 1 along with their probable mode of action and molecular targets.

FUTURE PROSPECTS & CONCLUSION

Although cucurbitacins are highly toxic compounds and often their biological activities are close to their toxic dose level, these compounds possess immense pharmacological potential. Apart from their toxic nature cucurbitacins have been proved to possess pharmacological effectiveness against inflammation, cancer, artherosclerosis and diabetes. The information on absorption, distribution, metabolism and excretion of these compounds is scarce and can be an area of exploration keeping in concern their toxic effects in mammals. The reports on their toxicity must not scavenge the probability of potential use of these compounds as potent medicinal agents. The chemical modification of various functional groups of these compounds to combat toxic effects may provide important lead compounds for future research.

Table 1.

Reported biological activities of cucurbitacins with probable mechanism of action

Activity	Mechanism	Reference
Antitumor activity (Cucurbitacin A, B, D, E, I, & Q analogues)	inhibition of Janus kinase/Signal Transducer Activator of Transcription 3 (JAK/STAT3) signaling pathway	[3]
	disruption of F-actin cytoskeleton.	[4]
	Down-Regulation of the c-Myc/hTERT/Telomerase Pathway and Obstruction of the Cell Cycle	[5]
Anti-inflammatory (Cucurbitacin B, D, E, I & R analogues)	inhibit the expression of TNF and proinflammatory mediators such as nitric-oxide synthase-2 and cyclooxygenase-2.	[6]
	inhibition of NO generation through blocking NF-$_{\kappa}$B activation	[7]
Artherosclerosis (Cucurbitacin B & E analogues)	Inhibition of lipid-oxidation products malonaldehyde (MAD) and 4-hydoxynonenal (4-HNE)	[8]
Blood circulation promoter (Cucurbitacin D)	Inhibition of Na^+/K^+-ATPase	[9]
Immunosuppressant (Cucurbitacin B)	By inhibiting expression of surface markers CD69 and CD25 required for activation of lymphocytes.	[10]
Antidiabetic	Activation of AMPK pathway (a major regulatory pathway for GLUT4 translocation)	[11]

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PROCEEDING -45

"NEEDLELESS VACCINE AND INJECTION" – TECHNOLOGY OF TOMORROW

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NEED OF NEEDLELESS VACCINE:-

Immunization programs are the most challenging health programs in developing countries like India. These programs are very difficult to conduct throughout remote areas due to deficiency of skilled medical persons. Reuse of needles which is a common practice in developing countries lead to transmission of disease like AIDS and hepatitis. These vaccine delivery system can increase speed of immunization in mass eradication programs and bioterrorism and reduce cost, discomfort and improve patient compliance also. Moreover vaccine are generally delivered to children, infant and some adults also who afraid of injection due to needle phobia or pain. A needle less vaccine provides painless vaccination [1, 2]. Discoveries in the field of needleless vaccines are great boon to such immunization programs. Skin act as one of the major route for needleless delivery. Jet injectors, transdermal patches, micro needles and deformable elastic vesicles are some of the methods for painless and needleless delivery.

International Journal of Pharma and Bio Sciences
ISSN 0975 - 6299

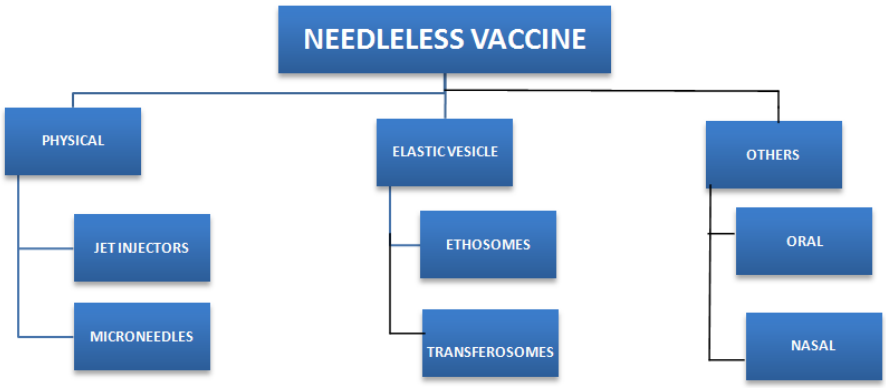

Figure 1.
Different types of Needleless vaccine

1. PHYSICAL METHOD

1.1 JET INJECTOR: - Jet Injector is one of the methods used for painless delivery of vaccines and biological products through skin. Jet injectors uses high pressure of gas or employ a high speed jet of liquid which force the powder or liquid to pass through skin like jet without the use of needle. These can be used for mass immunization program like influenza, Hepatitis B, cholera, smallpox, and polio, DNA immunization [4, 5, 6, 7]. Jet injector can deliver the vaccine efficiently into dermal, subcutaneously or intramuscularly depending on the pressure and properties of jet injector [2]. Multiple jet injectors were used in mass immunization programs due to their speed, cost effectiveness and needless delivery up to 1980. But due to little risk of transmission of disease due to backflow or splash back from patient or injector head may get contaminated [8] .So to overcome the issue of contamination disposable or single use jet injector came into existence.

1.2 MICRONEEDLE: - Microneedle is small needle 10–20 μm only in depth which deliver drug across stratum corneum. Influenza vaccine, Hepatitis B surface antigen has been delivered by microneedle. As microneedle do not reach deep epidermis or dermis are almost painless. These are of many types. Hollow micro needle are used for delivery like injection while another type of microneedle are coated with drug or vaccine and one more type in which microneedles are made up of polymer containing vaccines which get dissolve or release vaccine/ drug in skin [1, 11, 12].

2. ELASTIC VESICLE:-Various bilayer vesicles have been used for drug delivery of biological products and vaccines due to their ability of penetration and stability benefits. These can deliver vaccines by transcutaneous route having advantage of safe, painless, economical and delivery of vaccine on mass level.

2.1 TRANSFEROSOME:- Transferosome is one of the deformable vesicles used for drug delivery through skin. Transferosome are self optimized ultradeformable bilayer lipid vesicles which can tolerate ambient stress composed of edge activator (surfactant like Span 60, Span 80, Sodium cholate etc.) and phosphetidylcholine (generally soya PC or hydrogenated phosphetidylcholine) [13,14].These vesicles penetrate the stratum corneum by water flux generated on the skin due to amphiphilic phosphetidylcholine and deformability of vesicle provided by edge activator[14]. Mechanism of skin penetration is. Lipids and surfactants are dissolved in organic solvent and evaporated in rota evaporator. After this hydrate the dried layer with phosphate buffer with vigorous shaking [13, 14,].Characterization of Transferosome is done by observing particle size and morphology by Visualization of transferosomes can be Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM), Dynamic Light Scattering (DLS) and Photon Correlation Spectroscopy (PCS). Entrapment

efficiency of drug in transferosomes can be measured by the dialysis or ultracentrifugation technique. Confocal scanning electron microscopy (CSLM) is done to view penetration behavior of Transferosome [13, 14, 16]. Insulin, ketoprofen, Tamoxifen, Norgesterol, Interferon -2, Oestradiol, Hydrocortisone, Hepatitis B antigen, Lidocaine, Benzocaine, Colchicine are delivered by transferosomes [14].

2.2 ETHOSOMES: - These are elastic liposome having high amount of ethanol. These made up of phosphetidylcholine and high amount (20-45%) of ethanol. Ethosomes act by increasing the fluidity of lipid by interaction of ethanol with skin lipids and due to elasticity of these vesicles. Preparation and Characterization of ethosome is same as that of Transferosome [17].

CONCLUSION: - It can be concluded that alternative routes like transdermal or oral for vaccine delivery proved to be promising route for painless, needleless delivery. These techniques found to be very effective for mass immunization and protect the health worker from the risk of blood born diseases. Elastic vesicles provide stability as well as safe delivery of vaccines. Although research work has done on these techniques but still more work has to be done for the commercialization of these techniques.

Table1.
Examples of Needleless vaccine

S.No	Type	Example	Reference
1.	Oral vaccine	Polio, cholera , typhoid	9,10
2.	Jet Injector	Measles, Smallpox, Cholera, Polio, Influenza, Hepatitis B, DNA HIV	3,4,5,6,9
3.	Microneedle	BCG, smallpox, Influenza, Hepatitis B,	1,11,
4.	Transferosome	Tetanus, Hepatitis B, Interferon Bovine Serum Albumin,	13,14, 15,16
5.	Ethosome	Insulin, Minoxidil, Lamivudine	17

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PROCEEDING -46

Tocilizumab: A New Drug Candidate for the Treatment of Rheumatoid Arthritis

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INTRODUCTION:

Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease. The characteristic feature of this condition is persistent symmetric polyarthritis (synovitis) that affects hand, feet and any other joint lined by synovial membrane. Genetic factors and immune system abnormalities contribute to disease propagation. The underlying pathophysiology includes production of autoantibody (RA factor) by B cells and activation of T cells. It is marked by abnormal production of numerous cytokines, chemokines, and other inflammatory mediators (e.g., tumor necrosis factor alpha [TNF-alpha], interleukin [IL]–1, IL-6, transforming growth factor beta [TGF-beta], IL-8, fibroblast growth factor [FGF] and platelet-derived growth factor [PDGF]). The therapies currently used to treat RA include non-steroidal anti-inflammatory, disease-modifying anti-rheumatic drugs (DMARDs), biological-response modifiers and glucocorticoids. Efforts are made to develop biologic agents which are target specific and block pro-inflammatory mediators. Tocilizumab being an IL-6 receptor antagonist is a novel drug discovered for the treatment of rheumatism which was approved by FDA in January 2010.

MECHANISM OF ACTION OF TOCILIZUMAB:

International Journal of Pharma and Bio Sciences
ISSN 0975 - 6299

Tocilizumab (TCZ) is a recombinant humanized antihuman IL-6 receptor monoclonal antibody of the IgG1κ subclass. IL-6 is produced by T cells, B cells, lymphocytes, monocytes, and fibroblasts, and has a role in T cell activation and immunoglobulin secretion. TCZ binds to the alpha chain of both membrane-bound and soluble IL-6, thus blocking its signaling.

INDICATIONS:

Tocilizumab is used in the treatment of inflammatory arthritides - including rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis. It was approved in Japan for Castleman's disease a rare benign tumor of B cells. It is effective in combination therapy with methotrexate for the treatment of rheumatoid arthritis.

ADMINISTRATION AND DOSE:

The starting dose for tocilizumab is 4 mg/kg administered once every 4 weeks as a 60-minute single drip infusion, followed by an increase to 8 mg/kg based on clinical response.

CAUTIONS AND SAFETY PROFILE:

Adverse events most commonly reported in tocilizumab-treated patients include infections mostly upper respiratory tract infection, gastrointestinal perforation, hypersensitivity reactions, including anaphylaxis., headache, high blood pressure, and liver enzyme elevations. The laboratory changes include increased low-density lipoprotein cholesterol levels and decreased neutrophil and platelet counts. TCZ is contraindicated in patients with ongoing infections. Patients with family or past history of tuberculosis must undergo a thorough review. Monitoring of serum liver enzymes is recommended during TCZ treatment, especially when combined with MTX. Surgery can only be commenced14 days after the last infusion of the drug.

CONCLUSION:

Tocilizumab is a novel approach for the treatment of rheumatoid arthritis in the patients who failed to elicit sufficient therapeutic response with DMARD's and other biologic agents. However, the safety data is inadequate yet, hence, post- marketing surveillance is underway to make it a better and more concrete therapy.

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PROCEEDING -47

MICROEMULSION OF LOSARTAN

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INTRODUCTION

The present study was conducted to investigate the potential of microemulsions formulation of antihypertensive drugs losartan for transdermal delivery. Losartan is a common drug used for treatment of hypertension and are taken orally with dose ranging from 25-100 mg (tablets) for losartan [1].

Microemulsions are stable transparent dispersions of oil and water stabilized by an interfacial film of surfactant and cosurfactant molecules having a droplet size of less than 0.5 µm or 500 nm. In topical formulations, microemulsions

have been proved to increase the cutaneous absorption of both lipophilic and hydrophilic active pharmaceutical ingredients (API's) [2].

EXPERIMENTAL METHODS

Solubility Studies: The solubility of Losartan in various oils , surfactants, and cosurfactants was determined by adding excess of drugs in 4 mL of each of the chosen oils, surfactants, and cosurfactants. They were then kept at 37°C for 72 hours on a shaker. The vials were removed from the shaker and centrifuged at 3000 rpm for 15 minutes. The supernatant layer was analyticaly detected for the drug content (UV absorption at 230nm).

Preparation of microemulsions and construction of pseudoternary diagrams: Based on results of solubility studies, clove oil was used as oil phase, labrasol as surfactant, ethanol as cosurfactant and distilled water as aqueous phase. Pseudo ternary diagrams were constructed to investigate the Microemulsion formation regions, by titrating a series of Surfactant and cosurfactant (Smix) mixed in different weight ratios (1:0, 1:1, 2:1, 3:1, 4:1, 5:1and 6:1). For each S_{mix} ratio, oil and Smix were combined in different weight ratios from 1:9 to 9:1. Sixteen different combinations of oil and Smix (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1, 1:2,1:3,1:3.5, 1:8, 1:7, 1:6, 1:5), were prepared.

Stability studies: Out of sixteen titrations described above, the ones which gave only transparent emulsions with addition of aqueous phase were selected for further stability studies. Drug loaded Microemulsions (5 mg/ml of losartan which was kept constant in all the selected formulations) were subjected to different thermodynamic stability tests. (heating and cooling cycles, freeze-thaw cycle, centrifugation)

Characterization of microemulsions: pH and particle size determinations were carried out.

RESULTS AND DISCUSSION

Solubility studies: Maximum solubility of losartan was observed in Clove oil (oil phase), Labrasol (surfactant) and ethanol (cosurfactant).

Preparation of microemulsions and construction of pseudoternary diagrams: Care was taken to ensure that observations were not made on metastable systems—although the free energy required to form an emulsion is very low, the formation is thermodynamically spontaneous.

Thermodynamic Stability studies of Drug loaded microemulsions

Out of all the emulsions which were tested for stability, two emulsions remained stable after all the stability tests

Table 1: composition of stable Microemulsions of Losartan (5mg/mL)

	Ratio	Oil (µl)	S_{mix} (µl)	Water (µl)	Total (µl)	O%	S%	W%	Drug (mg)
L11	5:1 (1:9)	100	900 (S=750 CoS=105)	2350	3350	2.99	26.87	70.15	16.75
L12				3000	4000	3	23	75	20

Characterization of microemulsions

The pH of the microemulsions came out to be 5.9 for Losartan microemulsions. Among the two final microemulsions that passed through all stability tests, the average particle diameter sizes was 143nm with Poly Dispersity Index of 0.121 for Losartan.

SUMMARY

Stable microemulsions of losartan of nanometric size were successfully formulated. Further *in vitro* Franz Diffusion cell Studies need to be planned.

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