2. LITERATURE REVIEW:

A. PUNICA GRANATUM:

- Naqvi, S.A.H. et al. (2009) has studied the antiamoebic activity of water soluble fractions of the rind and flowers of *Punica granatum using in vitro* and in vivo studies, on a virulent strain of *Entamoeba histolytica*, exhibited encouraging results.

- Surinderkumar Y. et al. (2007) evaluated Antihepatotoxic Effect of *Punica granatum* Acetone Extract Against Isoniazid and Rifampicin Induced Hepatotoxicity. study has investigated the effect of 70% acetone extract of *Punica granatum* L. fruits on hepatic marker enzymes, antioxidants, and tissue peroxidative damage during isoniazid- and rifampicin-induced hepatotoxicity. These findings demonstrated the hepatoprotective potential of the acetone extract of *Punica granatum* fruits on tissue defense systems during isoniazid- and rifampicin-induced hepatotoxicity in rats.

- Fernando C.A., et al. (2006) performed In vitro susceptibility of *Entamoeba histolytica* and *Giardia lamblia* to plants used in Mexican traditional medicine for the treatment of gastrointestinal disorders. species showed selectivity and significant antiprotozoal activity were *Chiranthodendron pentadactylon*, *Annona cherimola* and *Punica granatum* were the most active on *Entamoeba histolytica* with IC50 <30_g/ml. *Dorstenia contrajerva*, *Senna villosa* and *Ruta chalepensis* were the most active toward *Giardia lamblia* with IC50 <38_g/ml. The potency of *Chiranthodendron pentadactylon* (IC50 2.5_g/ml) on *Entamoeba histolytica* was close that of to emetine, but far less than metronidazole, drugs used as control.

- Hye-Min K. et al. (2005) demonstrated β-Secretase (BACE1) Inhibitors from Pomegranate (Punicagranatum) Husk as anti-dementia agents. Two β-secretase(BACE1) inhibitors were isolated from the husk of pomegranate (Punica granatum) by activity guided purification and identified as ellagic acid and punicalagin. The compounds were non-competitive inhibitors with a substrate in the Dixon plot. Ellagic acid and punicalagin were less inhibitory to α-secretase (TACE) and other serine proteases such as chymotrypsin, trypsin, and elastase, thus indicating that they were relatively specific inhibitors of BACE1.

- Angel S.L. et al. (2007) studied anti-viral activity of whole fruit extracts of plant *Punica granatum* L.. This aqueous or hydroalcoholic extracts of whole fruits have proved highly
active against the influenza virus. However, some toxic properties of this extract have also been reported. In the present study, the genotoxicity of a Punica granatum (pomegranate) whole fruit extract was also assessed using different in vitro and in vivo assays that detect DNA damage at different expression levels. Results from reversion and gene-conversion test clearly showed that the hydroalcoholic extract of P. granatum whole fruits is genotoxic when tested both in vitro and in vivo.

- **Murthy K.N. et al. (2004)** Studied wound healing activity of methanolic extract of Punica granatum peels. The presence of a high content of phenolic compounds (44.0%) along with other constituents was reported. This extract was formulated as a 10% (wt/wt) water-soluble gel and was studied for its wound healing property against an excision wound on the skin of Wistar rats.

- **Kotamballi N. et al. (2002)** Studied Antioxidant Activity of Pomegranate (*Punica granatum*) Peel Extract Using in Vivo Models and demonstrated that peel extracts possess significant antioxidant activity in various in vitro models. methanolic extract of pomegranate peel at 50 mg/kg (in terms of catechin equivalents) followed by CCl₄ treatment causes preservation of catalase, peroxidase, and SOD to values comparable with control values, whereas lipid peroxidation was brought back by 54% as compared to control. Histopathological studies of the liver were also carried out to determine the hepatoprotection effect exhibited by the pomegranate peel extract against the toxic effects of CCl₄. Histopathological studies of the liver of different groups also support the protective effects exhibited by the MeOH extract of pomegranate peel by restoring the normal hepatic architecture.

- **Al-Zoreky N. S. (2009)** studied antimicrobial activity of pomegranate (*Punica granatum* L.) fruit peels against some food-borne pathogens by various extracts from pomegranate fruit peels using both *in vitro* (agar diffusion) and *in situ* (food) methods. The 80% methanolic extract of peels (WME) was a potent inhibitor for *Listeria monocytogenes*, *S. aureus*, *Escherichia coli* and *Yersinia enterocolitica*. The minimum inhibitory concentration (MIC) of WME against *Salmonella enteritidis* was the highest (4 mg/ml). WME afforded > 1 log₁₀ reduction of *L. monocytogenes* in food (fish) during storage at 4 °C. Phytochemical analyses revealed the presence of active inhibitors in peels, including phenolics and flavonoids. The activity of WME was related to its higher content (262.5 mg/g) of total phenolics.
Nam D. K, et al. (2002) demonstrated hemopreventive and adjuvant therapeutic potential of pomegranate (*Punica granatum*) for human breast cancer. Their actions, and of the crude whole oil and crude fermented and unfermented juice concentrate, were assessed *in vitro* for possible chemopreventive or adjuvant therapeutic potential in human breast cancer. The ability to effect a blockade of endogenous active estrogen biosynthesis was shown by polyphenols from fermented juice, pericarp, and oil, which inhibited aromatase activity by 60–80%. Fermented juice and pericarp polyphenols,

Hülya Orak H (2011) studied antibacterial and antifungal activity of pomegranate (*punica granatum* l.cv.) peels. The antibacterial activity of peel extracts was tested against three bacteria strains, which were named *Staphylococcus aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922) and *Salmonella Enteritidis* (ATCC 13076). The antifungal activity was tested against two fungal strains, which were named *Aspergillus parasiticus* NRRL 2999 and *Aspergillus parasiticus* NRRL 465. All extracts possessed remarkable antibacterial and antifungal activities against all tested bacterial and fungal strains.

Qna E..Y. et al. (2007) studied Antidiarrheal Activity of the aqueous extract of Punica granatum (Pomegranate) Peels. The antidiarrheal effects of the aqueous extract of Punica granatum L. (Punicaceae) peels were evaluated in rats. Studies were carried out on the isolated rat ileum, gastrointestinal motility in vivo, and on castor oil–induced diarrhea in rats. The results revealed that the extract exhibited a concentration-dependent inhibition of the spontaneous movement of the isolated rat ileum and attenuated acetylcholine-induced contractions. The extract (100, 200, 300, and 400 mg=kg) also caused a dose-dependent decrease of gastrointestinal transit and markedly protected rats against castor oil–induced diarrhea enteropooling.

Ajaikumar K.B. et al. (2005) studied the inhibition of gastric mucosal injury by Punica granatum L. (pomegranate) methanolic extract. Administration of 70% methanolic extract of Punicagranatum fruit rind (250mg/kg and 500mg/kg) shows a percentage of inhibition in 22.37, 74.21 and 21.95, 63.41 in aspirin- and ethanol-induced gastric ulceration, respectively. In treated groups of animals, the in vivo antioxidant levels such as superoxide dismutase (SOD), catalase, glutathione (GSH) and glutathione peroxidase (GPx) levels were increased and found
more or less equal to the normal values.

- **Yasoubi P. et al. (2007)** reported total phenolic contents and antioxidant activity of Pomegranate (*Punica granatum* L.) Peel extracts. The phenolic compounds of pomegranate (*Punica granatum* L.) peel extracted by two methods (solvent and ultrasound-assisted) with five solvents (acetone, methanol, ethanol, water and ethyl acetate) were compared with supercritical fluid extraction (SFE). The total phenolic compounds were determined according to the Folin-Ciocalteu reagent using tannic acid as standard. The overall results showed that acetone with sonication produced the maximum amount of phenolic compounds from pomegranate peel extracts (PPE).

- **Yuhao L. (2008)** studied that Pomegranate flower was a unique traditional antidiabetic medicine with dual PPAR-alpha/-gamma activator properties. PPARs are transcription factors belonging to the super family of nuclear receptors. PPAR-alpha is involved in the regulation of fatty acid (FA) uptake and oxidation, inflammation and vascular function, while PPAR-gamma participates in FA uptake and storage, glucose homeostasis and inflammation. The PPARs are thus major regulators of lipid and glucose metabolism. Synthetic PPAR-alpha or PPAR-gamma agonists have been widely used in the treatment of dyslipidaemia, hyperglycaemia and their complications. However, they are associated with an incidence of adverse events.

**B. AEGAL MARMALOSE :**

- **Uttam K. D. et al. (2006)** studied effect of aqueous extract of leaf of *Aegle marmelos* on testicular activities in rat. The aqueous extract of leaf of *Aegle marmelos* (Bael) at the dose 50 mg/100 g body weight resulted a significant diminution in the activities of key testicular steroidogenic enzymes along with low levels of plasma testosterone and relative wet weights of sex organs in respect to control without any significant alteration in general body growth. Germ cells numbers in different generation at stage VII of seminiferous epithelial cell cycle were diminished significantly after the treatment of the above extract. The above mentioned dose did not exhibit any toxicity in liver and kidney. Therefore, it may be predicted that the aqueous extract of leaf of *Aegle marmelos* has a potent antitesticular effect at a specific dose.

- **Kanokporn S. et al. (2006)** evaluated safety of aqueous extracts from *Aegle marmelos* and *Stevia rebaudiana* on Reproduction of Female Rats. The purpose of this study was to
evaluate the safety of a Thai medicinal plant, *Aegle marmelos*, and a non-caloric sweetener, *Stevia rebaudiana*, on the reproduction of female rats. Female rats were treated orally with aqueous extract of *A. marmelos* (6%) and *S. rebaudiana* at various concentrations (0, 0.2, 1, or 10%) for 60 days (1 ml/day) before mating. No notable abnormalities were observed in any of the pregnant rats. The number of corpus lutea, implanted and dead fetuses, as well as the sizes of the fetuses in the treated rats were not significantly different from those of the controls. Based on these results, it may be concluded that aqueous extracts of *A. marmelos* and *S. rebaudiana* at the concentrations used in this study do not alter the reproduction of female rats.

- **Rajesh K. et al. (2008)** studied insecticidal activity of *Aegle marmelos* (L.) Correa Essential Oil Against Four Stored Grain Insect Pests. Experiments were carried out to determine the potential of using essential oil from leaves of *Aegle marmelos* to control insect infestation of stored gram from *Callosobruchus chinensis* (L.) (Bruchidae) and wheat from *Rhyzopertha dominica* (F.) (Bostrichidae), *Sitophilus oryzae* (L.) (Curculionidae) and *Tribolium castaneum* (Herbst) (Tenebrionidae). After introducing the test insects, stored gram and wheat samples were fumigated with essential oil of *Aegle marmelos* at 500 μg/mL (ppm). The oil significantly enhanced feeding deterrence in insects and reduced the grain damage as well as weight loss in fumigated gram and wheat samples infested with all insects except *T. castaneum*. The essential oil at different doses significantly reduced oviposition and adult emergence of *C. chinensis* in treated cowpea seeds.

- **Sabu M.C. et al. (2004)** studied antidiabetic activity of Aegle Marmelos and Its relationship with Its Antioxidant Properties. The present study examined the action of Aegle marmelos against experimental diabetes as well as the antioxidant potential of the drug. A methanolic extract of Aegle marmelos was found to reduce blood sugar in alloxan diabetic rats. Reduction in blood sugar could be seen from 6th day after continuous administration of the extract and on 12th day sugar levels were found to be reduced by 54%. Oxidative stress produced by alloxan was found to be significantly lowered by the administration of Aegle marmelos extract.
● **Patil R. H. et al. (2009)** has studied **antifungal and antiaflatoxigenic** activity of Aegle marmelos Linn. The antiaflatoxigenic effects of ethanolic extract of the leaves of Aegle marmelos were studied on common aflatoxigenic fungal species. Aegle marmelos exhibited antifungal and antiaflatoxigenic activity at a concentration range of 0.5 to 2 mg/ml. The shake flask method was used to evaluate the antifungal and antiaflatoxigenic activity. The extract showed varied levels of antifungal and antiaflatoxigenic activity against the test fungi. Preliminary phytochemical tests of ethanolic extracts demonstrated the presence of major phytochemicals like phenols, tannins, flavonoids and alkaloids.

● **Mohammad Y.M. (2009)** studied clinical evaluation of antidiabetic activity of *Trigonella* Seeds and Aegle marmelos Leaves. He investigated clinically the antidiabetic activity of Fenugreek seeds (FG) (*Trigonella foenum-graceum Linn.*) and Bael leaves (BL) (*Aegle marmelos,Corr.*) individually and collectively in non insulin dependent diabetes mellitus (NIDDM) patients. There were significant changes in PPBGL of patients who were receiving these two herbs collectively as compared to the other patients who were receiving these herbs individually in comparison to patients who were on their standard oral hypoglycemic therapy.

● **Daswani P. et al. (2009)** has performed antidiarrhoeal activity on Aegle marmelos Unripe Fruit for Validating Its Traditional Usage. The hot aqueous extract (decoction) of dried unripe fruit pulp of A. marmelos for its antimicrobial activity and effect on various aspects of pathogenicity of infectious diarrhoea. The decoction was assessed for its antibacterial, anti diarridal and antirotaviral activities. The effect of the decoction on adherence of enteropathogenic Escherichia coli and invasion of enteroinvasive E. coli and Shigella flexneri to HEp-2 cells were assessed as a measure of its effect on colonization. It is significantly reduced bacterial adherence to and invasion of HEp-2 cells. The extract also affected production of CT and binding of both LT and CT to GM1. However, it had no effect on ST

● **Nadeem A. S. et al. (2011)** studied free radical scavenging and hepatoprotective activity of *Aegle marmelos* (Linn.) corr leaves against carbon tetrachloride. In the present investigation antioxidant and hepatoprotective activity of the methanolic extract of *A. Marmelos* leaves (MEAML) was examined on carbon tetrachloride (CCl4) intoxicated rats. The findings of the present investigation revealed that the MEAML possess significant hepatoprotective activity by suppressing ccl4 induced cellular oxidative stress.
Singana V. et al. (2007) has studied Hepatoprotective Effect of Bael Leaves (Aegle Marmelos) in Alcohol Induced Liver Injury in Albino Rats. The experiments were performed with four groups of animals. The experimental animals were administered with 30% ethyl alcohol for a period of 40 days and the fine crude plant leaves powder was fed to animals for next 21 days. The observed values of TBARS (Thiobarbituric acid reactive substances) in healthy, alcohol intoxicated and herbal drug treated animals were 123.35, 235.68 and 141.85 μg/g tissue respectively. The results were compared with the standard herbal drug silymarin (133.04 μg/g tissue). The experimental results indicate that, the Bael leaves have excellent hepatoprotective effect. A similar experimental result was also observed in other biochemical parameters.

Upadhya S. et al. (2004) studied hypoglycemic and antioxidant activity of Aegle marmelos in alloxan Induced diabetic rats. The present study was performed to evaluate the hypoglycemic and antioxidant effect of aqueous extract of Aegle marmelos leaves (AML) on diabetic rats. There was a decrease in blood glucose at the end of four weeks animals however it did not reach the control levels. There was an increase in erythrocyte GSH and a decrease in MDA. The plasma GST levels were raised in diabetic rats when compared to controls.

Kothari S. (2010) studied anxiolytic and antidepressant activities of methanol extract of Aegle marmelos leaves in mice. The objective of the present study was to evaluate the anxiolytic and antidepressant activities of methanol extract of Aegle marmelos (AM) leaves as well as its interaction with conventional anxiolytic and antidepressant drugs using elevated plus maze and tail suspension test in mice.

Yadav N.P. and Chanotia C.S. (2009) studied phytochemical and pharmacological profile of leaves of Aegle Marmelos Linn. Extensive investigations have been carried shown varied classes of compound viz., alkaloids, coumarins, terpenoids, fatty acids and aminoacids have been isolated from its different parts. Broadly, Aegle marmelos leaves contain alkaloids, Phenylpropanoids, terpenoids and other miscellaneous compounds whereas potential pharmacological activity of the leaves are hypoglycemic, anti-inflammatory, antimicrobial, anticancer, radioprotective, chemopreventive and anti-oxidative activity. Anhydroaegeline can be used as markerto standardize the plant material with respective to its potential anti diabetic activity.
• *Agung E. N. (2010)* studied effects of skimmianine, a quinoline alkaloid of *Aegle marmelos* correa roots, on the histamine release from rat mast cells. Skimmianine is a quinoline alkaloid isolated from the roots of *Aegle marmelos* Correa. The effects of skimmianine on the histamine release from rat mast cells was studied using two cell lines, rat basophilic leukemia (RBL-2H3) cell line, and rat peritoneal mast cells (RPMCs). DNP24-BSA, thapsigargin, ionomycin, compound 48/80 and PMA were used as inducers for histamine release from rat mast cell. Skimmianine markedly inhibited the histamine release from RBL-2H3 cells induced by DNP24-BSA, thapsigargin and ionomycin. The effect suggested is related to Ca2+ signaling since skimmianine showed strong effects when the histamine release induced by Ca2+ signal stimulants (thapsigargin and ionomycin). It is supported that skimmianine altered the influx of 45Ca2+ into the cells. In RPMCs experiment, skimmianine also suppressed the histamine release induced by Ca2+ stimulants, and phorbol myristate acetate (PMA). However, skimmianine had no effect on the histamine release induced by compound 48/80. Based on the results, the inhibitory effects of skimmianine on the histamine release from mast cells might involve some mechanisms related to intracellular Ca2+ signaling events and protein kinase C signaling possessing a main role in granule exocytotic processes.
1. **OBJECTIVE OF WORK:**

- The current status of the Helminthiasis reveals that 25-30% of world population is suffering from this and underdeveloped and developing countries like India, Sri Lanka, Pakistan and other sub-continent countries were having a major contribution to helminthiasis. On the other hand helminthiasis and subtype of helminthiasis are also affecting developed countries also and reports have estimated that not less than 200,000 people alone in the US population.

- The invasion of these worms does not produce the life threatening condition but surely affecting the normal lifestyle of the people. Infestation can cause morbidity, and sometimes death, by compromising nutritional status, affecting cognitive processes, inducing tissue reactions, such as granuloma, and provoking intestinal obstruction or rectal prolapsed and hence need proper treatment.

- The current medication available for the treatment of this disease are limited and as per the reports of WHO conventionally used benzimidazole derivatives are also showing the resistance in many cases in African countries.

- Beside this Office of Rare Diseases (ORD) of the National Institutes of Health (NIH) has listed Helminthiasis as a "rare disease" and this status has restricted the research on drug development in developing countries, that means newer molecules are not going to come from developed countries and its now responsibility of underdeveloped countries to find better treatment for helminthiasis.

- The treatment option presently available are Benzimidazol derivatives like Albendazole, Thibendazol, Metnizidazole, etc which is actually anti-protozoal category drug., but serving purpose because of limited choice of new molecules emerging out compared to other category of drugs. The current study is aimed towards initiating research towards this segment, which is need of underdeveloped and developing countries like India.

- The study is focused to find one or more phytochemical(s) which have a strong anthelmentic activity and can serve as lead molecule for further development.

- India is country perhaps the largest producer of medicinal herbs and is rightly called the botanical garden of the world. India has officially recognizes more than 3000 plants for
their medicinal value and it is generally estimated that over 6000 plants in India are used in traditional folk and herbal medicines, representing about 75% of the medicinal needs of the third world countries. Despite of thus till the date only few plants have been investigated thoroughly while a great number of plants being extensively used in medicines are still not investigated. Present work is also attempting to explore this Indian flora for anthalmentic activity specifically from Satpuda region. Many plants from this region are used by tribal peoples to cure the Helmenthiasis and to which they named as "Jant nashak". (Verbal communication)

- The plants *Punica granatum*, and *Eagle marmalose* are much promising plants for treatment of helminthes and this study is aimed to identify the potential of these drugs through scientific method with objective of getting new phytoconstituents for treatment.