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A Review of Active Chemical Constituents and Anticancer Activity of AEGLE Marmelos l. CORR. (BAEL)

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Abstract: Herbal medicine and medicinal plants have their roots deep embedded in our culture. One such plant is Aegle marmelos L. Corr. which is commonly known as Bael or Bel in India. The following review focuses on the various bio-active phytoconstituents present in Bael plant. It also aims to find out compounds of economic and medicinal importance in an attempt to isolate them for medicinal purposes. The other aim of this article is to review the potent anticancer activity of bael. The review encompasses an overview of both in-vitro ad in-vivo models of anticancer studies. The effect of leaves, fruit and bark are reported on various types of cancers and cancer cell lines such as leukaemia, papilloma, melanoma etc. This review also encompasses an indirect view towards cancer treatment. The intent of this article is to focus on the use of Bael plant in the future of cancer research, treatment and finding a cure.
Keywords: Aegle marmelos L. Corr., Anticancer, Anti-tumour, Antineoplastic, phytoconstituents, medicinal plants.

I. INTRODUCTION

India has a rich history which consists of herbal and plant based medicines. Ayurveda, one of the oldest texts in the world, consists of a plethora of these plant based remedies. The world knows and uses various Indian origin plants like- Holy Basil (Oscimum sanctum), Turmeric (Curcuma longa), Avla (Phyllanthus emblica), Hirda (Terminalia chebula), Behada (Terminalia bellirica) etc., for their medicinal properties which help treat various ailments. Hence, it can be inferred that these plants contain certain chemical constituents that give them their capacity of showing active biological effects. Hence, it becomes extremely important for us to study these plants in detail and isolate their active chemical constituents. One such plant, which is of high medicinal value, is Bael. All parts of this plant have been time and again used for their medicinal properties.

Bael- Aegle marmelos L. Correa belongs to the family Rutaceae[1]. It is mainly found in India and is also widely grown in Sri Lanka, Pakistan, Bangladesh, Burma, Thailand and most parts of Southeast Asia. Bael is a deciduous, subtropical, medium-sized tree with tri-foliate leaves. It bears fruits with multiple seeds which turn yellow-grey when ripe[1]. Various researches and clinical studies have proven that extracts of various parts of bael plant possess antidiarrheal, antimicrobial, antiviral, radio-protective, anti-cancer, antipyretic, anti-inflammatory, diuretic, anti-genotoxic, and ulcer healing properties[2]. A lot of research has been done in order to detect the chemical constituents which give this plant its miraculous properties. This review encompasses an overview of the active chemical constituents and the anti-cancer properties of - Aegle marmelos L. Correa.

A. Chemical Constituents

Almost all parts of the bael plant consist of active phytoconstituents. . Yadav and Chanotia have used the leaves of bael to determine its phytochemical and pharmacological profile. They reported that various classes of chemical compounds have been isolated from different parts of bael, viz. Alkaloids, Coumarins, Terpenoids, fatty acids and amino acids. They further worked with the leaves and concluded that leaves of bael contain Phenylpropanoids, Terpenoids, and other miscellaneous compounds which give them their potential pharmacological activity. Leaves show hypoglycemic, anti-inflammatory, antimicrobial, anticancer, radio-protective and chemo-preventive, and anti-oxidative activities. They further indicated the use of Anhydoaegeline as a marker to standardise the plant extracts for its potential anti-diabetic activity [3]. Charoensiddhi and Anprung studied the volatile compounds from the fruit of bael. SPEM/GC/MS studies revealed numerous compounds from the fruit. The compounds isolated were: Hexanal, Isoamyl acetate, Limonene, β-phellandrene, p-cymenne, Acetoin, (E)-2-octenal, (E,E)-2,4-heptadienal, dehydro-p-cymene, Linalool oxide, 3,5-Octadiene-2-one, α-cubebene, trans-p-mentha-2,8-dienol,Citronellal, β-cubebene, β-caryophyllene, Hexadecane, Pulegone, α-humulene, Verbenone, Carvone, Carvyl acetate, dihydro-β-ionone, E-6,10-dimethyl-5,9-undecadien-2-one, β-ionone, Caryophyllene

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oxide, Hexadecanoic acid and humulene oxide[4].Maity and colleagues studied the chemical constituents from various parts of the plant and their correspondin therapeutic effects. The following results were obtained[5]:

Part of plant:	Chemical constituent:	Therapeutic effect:
Leaf	Skimmiamine, Aegelin, Lupeol, Cineol, Citral, Citronellal, Cuminaldehyde, Eugenol, Marmesin	Anti-cancer, cardio-active, Anti-inflammatory, Anti-septic, Anti-allergic etc.
Fruit	Marmelosin, luvangetin, Aurapten, Psoralen, Marmelide	Cardio-protective, anti-ulcer, Heartbeat inhibitor, Anti-spasmodic, Anti-diarrheal
Bark	Immature- Marmin, Skimmiamine Mature- Fagarine	Abortifacient, Anti-ulcer, anti-diarrheal
Unripe fruit	Tannin	Astringent

We can see that bael has numerous active chemical constituents that give it its ability to help treat various ailments. A number of researches have proven the anticancer and antineoplastic activities of this plant.

B. Anticancer activity of AEGLE marmelos L. CORR

Cancer is one of the most life-threatening diseases of the new world. With more than 8.8 million fatalities in the year 2015 [6], it is now more important than ever to find new ways and methods of treatment for this deadly disease. The methods available today maybe more effective than their older counterparts, however, they have debilitating side effects. Hence, it is necessary now that we find methods to incorporate the modern techniques and our knowledge of Ayurveda to find treatment options that are more effective and have fewer side effects. Bael has shown anticancer activity and it is reviewed in this paper. Researches have been done in a direct and indirect manner, where in, effect of bael extracts were seen directly on the cancer cells or they were seen as cytotoxicity and on the harmful effects caused by cancer treatment options such as radio and chemotherapy.

C. Extract of leaves

50% ethanolic extract of Aegle marmelos leaves was used by Chockalingam and team to study its effect on Dalton's lymphoma ascites in Swiss albino mice. It was seen that the on injecting 200-400mg/kg of body mass of extract intraperitoneally, the increase in the body weight of the mice due to tumour growth was prevented and the mean survival time of the mice with tumours of the test group was increased as compare to those in the control group. Hence, it was concluded that A. marmelos leaf extract shows strong antioxidant and anti-tumour activity[7]. Another research by Alshatwi et al. shows the effect of methanolic leaf extract of A. marmelos Hepatocellular carcinoma, using $HepG_2$ cell lines. They used GC-MS analysis to find the major chemical components of leaves and they were reported as- Cinnamic acid, Methyl ester, 3, 4-dihydroxy-1(2)-Napthalenone, Phytol, Nicotiamide etc. Using $HepG_2$ cell lines it was established that, the test lines, which were treated with 5µg/mL concentration extract, showed growth supporting activity and its cell viability was 7.55% more than that of the untreated control. It was thus concluded that leaf extract of bael shows effective anticancer prospects and should be tested on various other cell lines[8].Bhatti and colleagues designed a study to carry the chemical standardisation and further the assesmement of anti-proliferative activity of leaf extracts. Alkaloids, Anthraquinone, Terpenoids etc. were reported in the alcohol and chloroform extracts and Tannins, Terpenoids and reducing sugars were reported in petroleum ether and Hexane extracts. Anti-proliferative activity was studied using human cancer cell lines of lung cancer (A-549), colon cancer (CoLo-05), ovarian cancer (IGR-OV-1), prostrate cancer (PC3), leukaemia (THP-1) and breast cancer (MCF-7). It was seen that the ethanolic extract shows maximum inhibition of breast and colon carcinoma cell lines and it also exhibited a good amount of anti-proliferative activity against leukaemia cell lines[9]. Diana Victoria T. and team conducted an in-vitro assay of crude acetone leaf extracts of A. marmelos and reported cytotoxic effects of the extract. An IC50 value of 116 µg/mL was shown by the ethanolic extract and 130 µg/mL was shown by ethyl acetate extract[10].Baskar et al. studied the use of leaf extracts of various plants to treat cancer. They used plants 10 plants which included: Cynodon dactylon, Tabermontana heyneana, Aegle marmelos, Costus speciosous etc. The plant leaves were sequentially extracted with hexane, ethyl acetate and methanol to obtain a crude extract, which was then, tested for its antioxidant abilities on colon adenocarcinoma (CoLo 320 DM) cell lines. The extracts induced apoptosis in the cancer cell lines. The study indicated a need for further research by isolating active constituents from these

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plant leaf extracts can show promising results in the future of cancer research[11]. Jagetia, Venkatesh and Baliga studied the effect of 50% ethanolic extract of A. marmelos leaves on Ehrlich ascites carcinoma transplanted Swiss albino mice. The extract was delivered intraperitoneally and orally to two different sets of mice. It was seen that the best results were obtained when the extract was injected intraperitoneally rather than the oral route. 400mg/kg dosage was found to be the best dosage and mice in this group showed a survival rate of up to 43days post tumour inoculation as compared to the saline treated control group where there were no survivors. Also, the acute toxicity study was done ans it showed that the drug was non-toxic up to 1750mg/kg[12].were: leukaemia (K562), T-lymphoid Jurkat, B-lymphoid Raji, Erythroleukaemia (HEL), Melanoma (CoLo38), and breast cancer (MCF7 and MDA-MB-231). Three derivatives- Butyl p-totyl sulphide, 6-methyl-4chromanone and butylated hydroxyanisole; showed suppressing of thein-vitro cell growth of human K562 cell lines. The anti-proliferative activities of the extracts were found to be on power with anti-tumour drugs like cisplatin, chromomycin etc.[13] Singh, Banerjee, and Rao studied the effect of 80% ethanolic extract of Bael leaves on carcinogen metabolising enzymes, which had caused free radicle damage in mice. The results showed significant increase in acid soluble sulphydryl content, cytochrome P450, NADPH-cytochrome, glutathione etc. It also decreased the activity of lactate dehydrogenase and formation of malondialdehyde in liver; further suggesting protection against oxidant induced membrane damage. The significant changes in drug metabolising enzymes and anti-oxidation levels strongly suggest that A. marmelos has a potential chemo-protective activity, especially against chemically induced carcinogenesis[14].

D. Extract of fruit

Sain and team isolated β-caryophyllene and Caryophyllene oxide from the fruit extract of A. marmelos using GC-Ms techniques. The effect of these fractionated extracts were then examined on Jurkat and neuroblastoma (IMR-32) cell lines. It was noted that β-caryophyllene and Caryophyllene oxide fractioned extracts of A. marmelos coaxed apoptosis in Jurkat cell lines. It was further noted that with some modification, this extract can act as a strong anti-inflammatory agent and induce apoptosis in neuroblastoma and lymphoma cell lines[15].Patel and Asdaq studied cellular immunity by neutrophil adhesion test and carbon clearance assay in albino mice. The study indicated significant increase in adhesion of neutrophils and also an increase in phagocytic index. Hence, it was suggested that A. marmelos fruit extracts have a potential of reinforcing the immune system[16] and hence giving it a better chance of fighting against neoplastic cells.

E. Extract of bark

Gupta et al. studied the chemo-protective and antioxidant effects of hyromethanolic extracts of *A. marmelos* bark. The effect was studied with the help of 7, 12-dimethylbenzeanthracene (DMBA) induced skin papilloma in Swiss albino mice. In this model a significant reduction in tumour burden, tumour incidence,and numer of papilloma was seen. After thecompletion of assay reduced SGH level was estimated in the control, carcinogen control and test groups, which was found to be reduced in the test group as compared to the carcinogen control group. Hence the bark extract was suggested to have anti-tumour and antioxidant potential against skin papilloma[17].

F. Miscellaneous

Gangadevi and Muthumary studied the effect of Taxol, which is produced by ungus Bartalinia robillardoides Tassi and was isolated from A. marmelos. Taxol showed strong cytotoxic activity towards BT220, H116, Int-407, HLK-210 and HL251 cell lines, which were tested in-vitro via apoptotic assay[18]. Walia, Kumar, and Kaur studied the anti-genotoxic activity of bael fruit extracts. This study suggested that the various polyphenolic compounds present in the fruit extract, result in its anti-genotoxic effect[19], thus resulting in a potential for chemo-protective and anticancer research.

II. CONCLUSION

Cancer, being a highly virulent disease, makes it important that more and more treatment options are researched and employed to combat the fatalities. Chemotherapy and radiotherap have made more progress in the past decade and are constantly opening new horizons in search of a cure. It hence becomes imperative that we use our centuries old knowledge of herbal medicine and strive to find a cure. Aegle marmelos is a marvellous plant with extraordinar anticancer properties. The aim of this review is to make a note of all the research done with is this plant and to note new scopes of research in order to combat this deadly disease with a better view.

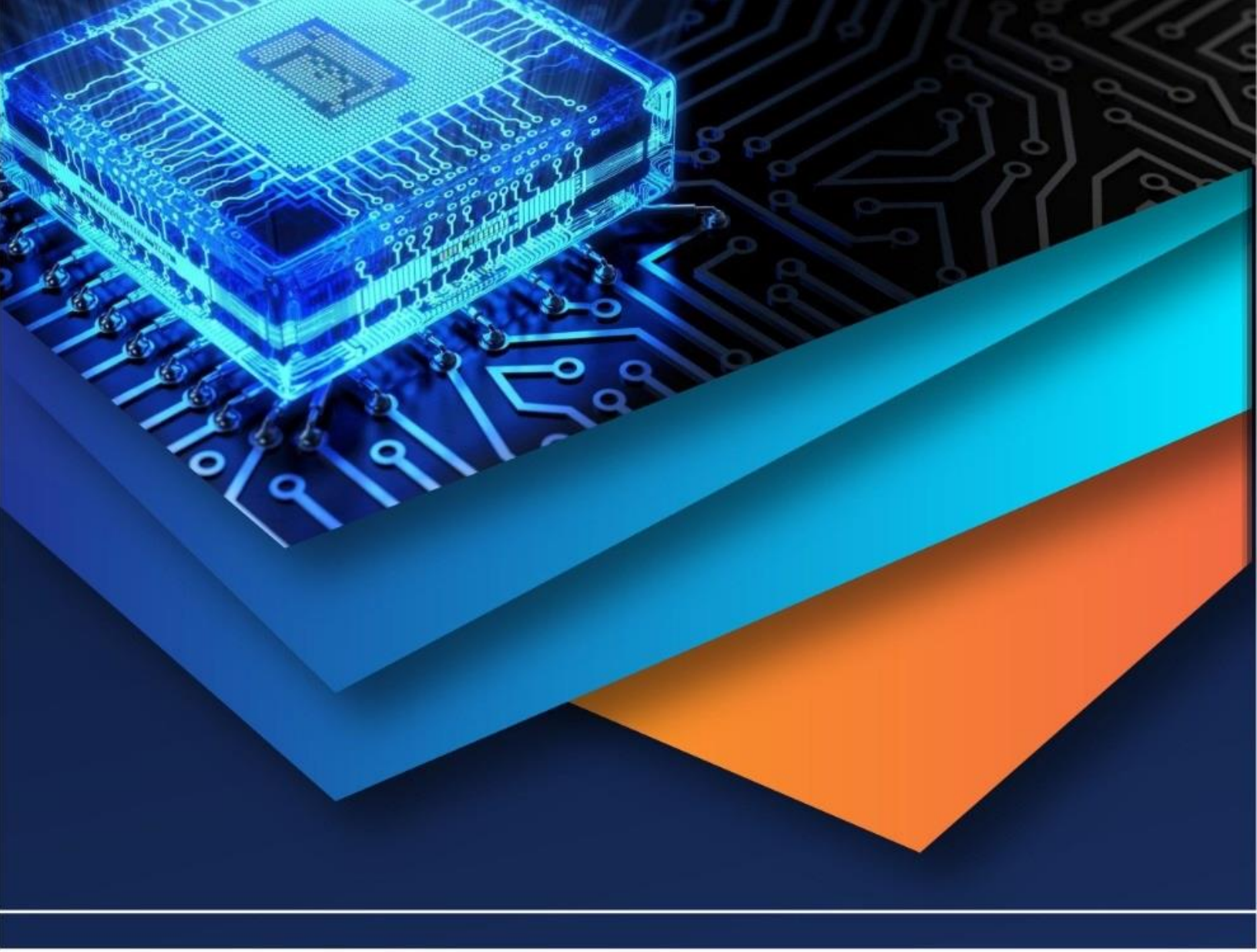
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