Review Article

Ethnopharmacological Relevance of *Aegle marmelos* (L.) Correa for Treatment of Diabetes Mellitus: A Review.

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ABSTRACT

Ayurveda, since time immemorial, have documented the use of *Aegle marmelos* (AM) for use in treatment of diabetes. With an ever growing population of diabetics in the world there is a requirement of effective management and treatment strategy for the disease. AM represents a promising candidate due to its proven anti-diabetic potential as well as ability to prevent many of the secondary outcomes associated with chronic hyperglycemia. Many compounds have been isolated from AM and structures elucidated, however, there lies a gap of validating each and every compound for its anti-diabetic potential. This review exclusively focusses on anti-diabetic property of AM plant parts extract and presents an exhaustive pre-clinical evidence of in vivo experiments conducted on chemically induced diabetic rats. The attributes of AM plant extracts advocates that this plant presents a strong candidate for the treatment of diabetes based on validation of traditional beliefs.

Keywords: Ayurveda, AM plant parts extract, diabetics.

INTRODUCTION

Aegle marmelos (L.) Corr. (AM) commonly known as *Bael* (Hindi), family Rutaceae is an important ethnomedicinal plant that has been in use for treatment of various ailments for over 5000 years. The roots, leaves, stem, bark, fruits as well as the seeds are used in the ancient Ayurveda [1]. Use of parts of the plant for treatment of a myriad of ailments such as chronic diarrhoea, peptic ulcer, dysentery, inflammation [2] and diabetes is documented[3-6]. A number of studies have scientifically validated the therapeutic potential of parts of the plant in having antipyretic [7], antihyperlipidemic, antifungal [8], antioxidant and free radical scavenging activity [9-13], hepatoprotective [14,15], cardioprotective, anticancer as well as radio-protective properties [5,16]. Moreover, anti-diabetic property of fruits and leaves of the plant is widely studied using *in vitro* and *in vivo* models.

Diabetes being a silent epidemic and a major global health concern requires intensive research attention in finding a cure or efficient management of the disease. According to the WHO Global Report on Diabetes 2016, estimates of 422 million adults were living with diabetes in 2014 compared to 108 million in 1980. In 2012 an estimated 1.5 million deaths were reported and the figure is much higher if fatalities associated with increased blood sugar is accounted. The prevalence of the disease has risen much faster in low and middle-income countries as compared to high-income countries [17]. Diabetes mellitus (Type II diabetes) is managed by different pharmacological and non-pharmacological means of intervention. Recently, there is a growing awareness in the use of functional foods and traditional medicine for effective management of the disease and its associated complications[18,19]. Out of the many plants with anti-diabetic activity, AM presents as one of the promising candidate that has functional bio-nutrients for glycemic control. For the first time, this literature review compiles the pre-clinical evidences on anti-diabetic property of bark, leaves and fruits of (AM).

Phytochemicals Identified from *Aegle marmelos*

Fruits of the plant contains important nutraceuticals such as phenolics, flavonoids, alkaloids, tannins, terpenoids, carotenoids and coumarins [20,21]. Some of the alkaloids present in AM fruits are skimmianine, fagarine, aegelin, aegelinosides A and anhydromarmelin. Carotenoids such as β-carotene and Vitamin A are also isolated from the fruits of AM. Other bioactive coumarins such as aegeline, aegelenine, marmin, marmelosin, marmelide, marmesin, aurapten, psoralen, luvangetin and umbeliferone as well as Flavonoids like anthocyanin and leucocyanin are also found. Moreover, terpenes such as citral, D-limonene, menthol, α-pinene, β-pinene and camphor are also reported to be present in plant parts of AM [1,20,21].

Biological Activities of *Aegle marmelos*

Carbohydrate metabolism

Control of carbohydrate metabolism and sustained release of glucose postprandial is one of the therapeutic strategy of management of T2DM. Inhibition of α-glucosidase as well as pancreatic α-amylase results in considerable delay in release of glucose that can be absorbed by the intestinal wall leading to control of spike in blood glucose concentration after a carbohydrate rich diet. Inhibitors like acarbose and voglibose considerably reduces the progression of T2DM as well as associated complications such as neuropathy, retinopathy and nephropathy[22].

In a study by Ansari et al., 2017, it has been revealed that the extract of AM has the potential to inhibit α-amylase and intestinal disaccharide function and can retard glucose absorption. Treatment of chemically induced T2DM rats with AM fruit extract showed remarkable suppression of serum glucose elevation after oral administration of sucrose at 2.5g/Kg body weight[23]. Hitherto another earlier study by Adisakwattana, 2014 on α-amylase and intestinal glucosidase inhibitory activity of five selected plant extracts, it was found that the inhibitory activity of AM fruit extract was low with IC_{50} > 5 mg/ml compared to other plant extracts from mulbery, butterfly pea, chrysanthemum and roselle [22]. However, synergistic effect could be observed when extracts of roselle and AM were combined.

Glucose uptake

Inability to utilize available serum glucose by cells of the body is an insignia of T2DM. The condition may be due to insulin resistance in which cells are unable to take up glucose despite the presence of insulin. One way of therapeutic management of T2DM is to enhance serum glucose utilization, as for instance the commonly used drug metformin enhances glucose uptake by cells with the available insulin in our body. In a similar manner, studies on AM plant extracts have shown to enhance serum glucose utilization by lowering insulin resistance. A study by Mudi SR et al., 2017 with aqueous extract of AM fruit and leaves indicated significant hypoglycemic activity in streptozotocin induced T2DM rat models. The enhanced glucose utilization potential of AM leaves extract can also be attributed to an alkaloidal-amide, aegeline [24,25], which stimulates glucose uptake through the Akt and Rac1 dependent pathways in muscle cells [26]. In yet similar studies by Kumar V et al., 2013 and Ramesh B, 2007 using umbelliferon, decrease in fasting serum glucose concentration was observed in a similar manner as seen with glibenclamide in a dose and time dependent manner [14,27].

Kesari et al., 2006, made similar observation with aqueous extract of AM fruits when administered at dose of 250 mg/kg on diabetic rats. The blood glucose level dropped by 35.1% in normal healthy rats within 6 hours and a significant decrease of 41.2% in diabetic rats after 2 hours. Moreover, continuous administration of AM fruit extract on severely diabetic rats (FBG> 250 mg/dl) for 14 days resulted in reduction of fasting blood glucose level by 60.84% compared to their pre-treatment level[28]. Kamalakkannan N and Prince PS, 2005 also observed hypoglycemic property of AM fruit aqueous extract on streptozotocin induced diabetic rats. The crude extract works better than glibenclamide in controlling blood sugar[29, 30].

Glycation of Haemoglobin

Prolonged exposure to elevated serum glucose concentration leads to glycation of haemoglobin of RBC and other cellular proteins and has the potential to alter cellular function. Product of advanced glycation (AGE) results in nephropathy, neuropathy as well as damages blood vessels. Moreover, accumulation of glycated proteins can also lead to DNA damage which are irreversible. Therefore, prevention of protein glycation is one of the strategies to prevent vital organ damage in diabetic patients.

Hafizur RM et al., 2017 conducted an extensive study on the anti-glycation property of AM fruit extract. Oral administration of 400 mg/kg AM extract significantly reduced HbA1C formation in streptozotocin induced diabetic rats and also reduced circulating AGE [31]. Earlier, anti-glycating activity of AM extracts were reported by Kamalakkanan et al., 2003, Gandhi GR et al., 2012, Panaskar et al., 2013, and Kumar V et al., 2013[32 12,14,25].

Kumar V et al., 2013 attributed the reduction in HbA1C in diabetic rats to umbelliferon isolated from dried stem bark of AM. Treatment with 10, 20 and 40 mg/kg of umbelliferon or 10 mg/kg glibenclamide significantly reduced HbA1C in diabetic rats compared to control [33]. In another study by Panaskar SN et al., 2013, with chloroform extract of leaves of AM, limonene was identified to possess anti-glycating activity [12]. Similar result of anti-glycating potential of AM bark extract was reported by Gandhi GR et al., 2012 [25]. However, the authors used crude AM bark extract at 200 and 400 mg/kg and did not attempt to identify the bioactive compound unlike Kumar V., et al., 2013.

Improvement of β-cell function

The most common first line drug of diabetes mellitus is metformin which promotes efficient utilization of serum insulin as well as moderate sugar absorption. Restoring the functionality of pancreatic β-cells for production of insulin would result in less drug dependence and reversal of the disease. There is no such clinically proven medication available to the T2DM patients and exploring traditional dietary phytonutrients may be an option. In line with traditional Ayurveda system that claims AM as a candidate for management of diabetes, several studies have reported increased secretion of insulin by pancreatic cells in chemically induced diabetic rats[15,25,31,34].

Kamalakkannan N and Prince PS., 2005 reported significant increase in insulin secretion and restoration of pancreatic cell function when streptozotocin induced diabetic rats were treated with AM fruit extract at 125 and 250 mg/kg twice daily for 30 days [34]. The study suggests a protective effect of the extract on pancreas. In contrast to the other observations Mudi SR. et al., 2017 did not observe any significant change in β- cell function compared to normal with AM leaves and fruit aqueous extract [35].

Prevention of secondary complication

Prolonged exposure to high serum glucose level has many secondary complications such as neuropathy, nephropathy etc. A method of controlling glycemic level

in the blood of diabetic patients inadvertently has a preventive effect on other medical complications associated with diabetes. Bhatti R et al., 2013 studied AM leaf extract on alloxan induced diabetic rats and found that treatment with a dose of 200mg/kg markedly reversed the morphological derangement of glomerulus caused by the drug [36]. They also observed increase in the renal reduced glutathione as well as catalase. Histologically, AM leaves extract could reduce glomerular expansion and dialation of the tubules. Similarly, Panaskar SN. Et al., 2013 earlier attributed limonene isolated from leaves of AM as a kidney protective compound[12].

Prevention of secondary complications of AM is also indicated by its anti-cataractous nature studied by Sankeshi V et al., 2013 in streptozotocin induced diabetic rats and in ex vivo lens organ culture. Ethyl acetate extract of leaves of AM could significantly reduce the function of aldose reductase, which is a key enzyme of polyol pathway that results in sorbitol accumulation. Moreover, α-crystallin from AM treated diabetic rats showed improved chaperone activity compared to control[10]. They also observed reduced opacification of lens which establishes a protective role of ethyl acetate AM leaves extract on cataract. Similar report was made by Panaskar et al., 2013 with chloroform extract of AM leaves extract and identified the protective compound to be limonene [12].

Acidosis and hyperglycemia leads to dysfunction of neurotransmitters and affects the central nervous system. In a manner of being in a vicious cycle, acetylcholine which is produced by the autonomous nervous system interacts with muscarinic M1 receptors of the CNS and stimulates insulin production [37]. It has been reported that there is reduction in muscarinic M1 receptors in the cerebral cortex, brainstem, hypothalamus and islets of the pancreas in streptozotocin induced diabetic rats [37,38]. Therefore, increase in muscarinic M1 receptors in the CNS and islet cells of pancreas would enhance secretion of insulin.

In a study by Gireesh G et al., 2008, using AM leaves extract it was reported that treatment of streptozotocin induced diabetic rats with AM leaves extract increased expression of muscarinic M1 receptors[39]. In an *in vivo* study, administration of 1 g/kg of AM leaves extract for fourteen days reversed the effect of streptozotocin induced diabetes on decreased muscarinic M1 receptors. They also observed increased mRNA expression of the receptor in AM treated diabetic rats.

Antioxidant and anti-dyslipidemic property

State of hyperglycemia is associated with increased oxidative stress of the cells leading to a number of complications. Many studies have pointed out that chronic hyperglycemia is associated with decreased anti-oxidant capacity and increase in free radicals. This may be due to inability of the body's antioxidant capacity to tackle the surge in release of free radicals, hence needing support of antioxidants from external sources. Prevention of oxidative damage to cells would act as a protective nature to vital organs. In line with the anti-hyperglycemic potential of AM extracts there are reports of its antioxidant [9 10,11,33] and anti-dyslipidemic potential [24,28,40].

Limonene, a bioactive compound isolated from AM leaves extract presented a DPPH scavenging activity of upto 85.26% and has shown to prevent formation of HbA1C. Kamalakannan N and Stanley, 2003 observed increased activities of catalase, superoxide dismutase and glutathione peroxidase in streptozotocin induced diabetic rats with treatment of 250 mg/kg of AM fruit extract[30]. Similarly, Sabu MC and Kuttan R, 2004 also reported antioxidant property of AM leaves extract on alloxan induced oxidative stress in rats. They observed increased activity of catalase, superoxide dismutase and glutathione peroxidase along with decreased lipid peroxidation, hydroperoxide and conjugated diene level in the serum [11]. Extract of AM leaves and fruits are shown to possess anti-dyslipidemic properties.

DISCUSSION

Diabetes being a major health concern for both developed and developing countries requires attention of healthcare professionals and policy makers equally. Use of allopathic medicine is the most common practice for management of the disease. With increase in awareness of traditional knowledge based medicines and simultaneous growth of analytical scientific research, a new era of rediscovering effective biomolecules have arrived. Based on traditional knowledge of Ayurveda, numerous scientific researches are carried out to find out and validate bioactive molecule(s). In the context of diabetes, AM presents a promising candidate for the management of the disease.

With the scientific evidence that we have it can be said that AM extracts possess anti-diabetic potential and also has properties that are useful for prevention of secondary health outcomes associated with the disease. However, most of the available studies seem to focus on crude extract of the plant parts rather than finding the effective molecule. Using crude extracts has its pros and cons as there can be synergistic effect of available biomolecules or may possess a compound that promotes cytotoxicity that can render the actual bioactive compound unfit for consumption in a crude form. In few of the studies covered in the review, the authors used purified compounds to assess bioactivity against diabetes. As for instance eugenol, aegelin, umbelliferon and limonene are studied for their potential. Though eugenol, aegelin and umbelliferon are evaluated separately for their anti-diabetic potential a combinatorial study that would reveal the additive, synergistic or antagonistic effect is not performed yet. Moreover, determining molecular events would help in understanding a detailed mechanism of action of the isolated compounds.

Since crude extract of AM possess β-cell regenerative capacity in streptozotocin induced diabetic rats it need to be looked into if the extract can revert diabetes in human subjects. However, a problem of setting appropriate dose may arise as 200 mg/kg used in mice will translate to 13 g of crude extract of AM in an average human of 65 kg body weight. Therefore, focussing on a purified compound for regenerative capacity will be a better choice.

Moreover, AM marmelos has many varieties, 17 of which is reported. None of the publications that is used in the literature review have described about the variety that is used in the study. Hence, we also need to verify if the bioactive principles are equally present in the common varieties that are consumed. Further analysis of bioactive purified components for their anti-diabetic effect need to be conducted.

CONCLUSION

AM fruit, leaves and bark extract presents a promising traditional medicine based anti-diabetic product. With available evidence from *in vitro* and *in vivo* studies it can be affirmed that AM extract has anti-glycemic, anti-dyslipidemic, β-cell regenerative as well as neuroprotective properties.

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