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Ayurvedic Dravyaguna (Pharmacological) Correlates with Biological Plausibility for antidiabetic activity of *Eujenia jambolana* Linn

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Abstract

***Eujenia jambolana* Linn (*Jambu* / Black plum; EjL) was found to be a frequently used medicinal plant in our earlier study of Marketed Ayurvedic Antidiabetic Formulations. Ayurvedic *dravyaguna* rationale and Biological Plausibility (BP) of EjL for anti-diabetic activity are currently reviewed in view of developing a new drug candidate for type 2 diabetes mellitus using Reverse Pharmacology. Classical and emerging Ayurvedic literature as well as modern pharmacological literature of EjL were reviewed here for *Ayurvedic properties* and biological plausibility foranti-diabetic potentials.**

Key Words: **Indian medicinal plants, *Dravyaguna* rationale, Biological plausibility, diabetes, Ayurvedic Pharmacoepidemiology, *Jambu, Eugenia jambolana*.**

Conflict of Interest: **None**

Introduction

During last several decades, new approaches and scientific paths for research in integrative Ayurveda have been evolved[1]. These paths include Ayurvedic Pharmacoepidemiology (AyPE)[2], Observational Therapeutic[3] Studies, Reverse Pharmacology[4], Ayurgenomics[5], Reverse Pharmacognosy[6], Ayurceuticals[7], Ayusoft[8] and Network Pharmacology[9]. However, there is a relative paucity of critical review of correlation of dravyaguna of a plant and diverse experimental and therapeutic data on selected medicinal plants e g. *medohara* and *lekhaniya* properties of *Commiphorawightii*[10]. Such correlates can open up new avenues for R&D of Ayurvedic plants with meaningful hypothesis.

In our earlier AyPE study, *Eujenia jambolana* Linn (*Jambu*/ Black plum; *E jambolana*) was found to be frequently used ingredient in Marketed Ayurvedic Antidiabetic Formulations[11]. Out of 180 formulations *E jambolana* was found as an ingredient in 113 (62.8%). Different parts of the plant were incorporated in varying concentrations and in different recommended dosages. Recently, CCRAS has also launched an Ayurvedic formulation that contains seed powder of *E jambolana*[12]. Almost a century back an eminent vaidya

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Mayaram Sundarji had recommended *E jambolana* seeds for *Madhumeha* as well as its one of the phytoactives viz. gallic acid[13] (fig1.) Around half a century back a placebo-controlled trial of the seed powder of *E jambolana* showed the reduction in glucose tolerance test in diabetic patients. The anti-hyperglycemic activity was also confirmed in animal diabetic models at Ciba Geigy Research Center [14].

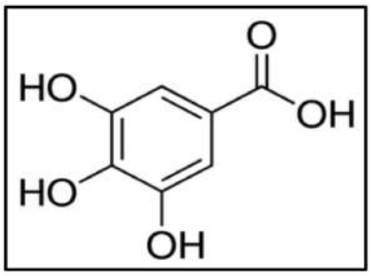


Fig 1. Gallic acid (3,4,5-trihydroxy-benzoic acid $C_6H_2(OH)_3COOH$)

E jambolana has been selected for the present review on correlations of dravyaguna with biological antidiabetic plausibility. In view of the need to address multiple targets besides hyperglycemia, the diversity of Ayurvedic properties of the plant can be reviewed for integrating the available phytopharmacological data.

Dravya Guna Vidnyan approach towards Pramehaghna Dravya

Dravya Guna Vidnyan is the branch of Ayurvedic sciences which deals with Identification, synonyms, properties and activity of the medicine [15]. Physiology of the human body, pathogenesis of the disease and the activity of the medicines revolve around the *tridoshas* and their harmony. Balanced *doshas* maintain the health. Aggravation and vitiation of *doshas* and their accumulation in respective *dhatus* (*Sthansanshraya*) are the basic characters of pathogenesis in any disease. In case of *Prameha* (*kaphaja prameha*; metabolic syndrome/ pre-diabetes) *Tridoshas* with *kapha* dominance are vitiated and get lodged in *Medodhatu* leading to over hydration (*Bahu-drava-shleshma*) and looseness of adipose tissue (*Abaddhavruddhi of Medadhatu*). As a matter of effect, metabolism gets deranged and increased subtle watery metabolic waste (*kleda*) is excreted through frequent urination. To reverse this pathology, medicines (*dravya*) with *kashaya rasa* (a stringent taste), *katu-vipak* (after digestion effects like pungent principle) and *laghu, ruksha* (light and dry) properties based substances are prescribed which will reduce *dravatwa* of *kapha* and *abaddhatwa* of meda thereby correcting the metabolism of *medovahasrotas*. In case of *madhumeha*, *vata* dominates over *kaphadosha* as a result *madhura-vipaki* and *bruhaniya* (muscle strengthening) *dravyas* are required to be introduced in the management to pacify *vata dosha*[16].

Biological Plausibility of Targeted Antidiabetic Activity

Many *in-vitro* and *in-vivo* basic studies of medicinal plants are now conducted in various animal models of diabetes[17] establishing the biological plausibility of these plants.

The term biological plausibility denotes an association between a presumed cause and subsequent result. It is considered as reliable with existing biological and medical knowledge; biologically believable. The term has originated in epidemiological research that has proved the association of tobacco- smoking and lung cancer[18]. The criteria proposed by Sir Austin Bradford Hill in 1965, states that plausibility is one of an important part of the method of reasoning- the reason, providing a possible biological mechanism[19]. It gives an epidemiological proof of a causal relationship; however that needs a number of explanations to confirm the association. Analysis of observations made at different levels of biological organization is needed to establish the biological plausibility of natural product. Gamalielsson *et al*. have proposed a method to assess biological plausibility of regulatory hypotheses using prior knowledge in the form of regulatory pathway databases[20]. Prior knowledge of such natural products is available in India. The hint and hits developed from AyPE / bed side-observational studies will help in conducting experiential phase of 'Reverse Pharmacology' studies. The approach of convergence of biological plausibility and Ayurvedic rationale as one of the methods of AyPE would add value to the drug discovery and development.

Biological Plausibility of *E jambolana*

Numerous *in-vitro* and *in-vivo* studies of *E jambolana* have been conducted to assess its antidiabetic activities. Several diabetic animal models, such as streptozotocine and alloxan induced diabetes; special diabetic strains etc have been used. Studies also have reported its preventive and protective properties for various diabetes related co-morbidities e.g. gastro-protective, cardio-protective, hepato-protective, anti-hyperlipidemic, anti-atherosclerotic, reno-protective and anticancer activity. Methanolic extract of seeds showed significant antioxidant effect against DPPH and H_2O_2 radicals scavenging activity with IC_{50} of 350 μg/ml[21]. Significant anti-inflammatory activity of ethyl acetate and methanol extracts of leaves (200 and 400 mg/k orally) have been observed in carrageenan induced paw oedema in wistar rats[22]. Aqueous extracts of seeds significantly inhibited α-amylase, α-glucosidase, and activities in a dose dependent manner in invitro[23]. Ethanolic seed extract showed hypolipidemic activ-

ity[24] and ethanolic fruit extract has shown a significant reduction in serum ALT, AST and CPK level in male albino rats in dyslipidemic rats[25]. Franca *et al* reported anti-hypertriglyceridemic effect of the hydroethanolic extract of leaf (0.5 or 1.0 g/kg/day) in obese rats and supported the new mechanism of action of antihypertriglyceridemic effect[26]. Pre-treatment (for 30 days) of hydro alcoholic extract of fruit pulp (400 mg/kg) daily showed cardioprotective activity by reducing cardiac markers (serum glutamate oxaloacetate transaminase, creatine kinase-myocardial band, cardiac troponin I), markers of inflammation (interleukin-6, C-reactive protein, and tumor necrosis factor alpha); and increased levels of superoxide dismutase significantly (Shulka SK)[27]. Behra et al reported nephroprotective effect of aqueous extract of seed (500mg/kg/orally/120 days) in diabetic rats[28]. It not only decreased serum creatinine and blood urea significantly but histology of kidney also improved. Antihypertensive activity of hydroalcoholic extract of leaves (0.5g/kg/day)[29], anti-atherosclerotic activity (α-hydroxysuccinamic acid) of fruit pulp[30], anticoagulant and antiplatelet effects (Methanolic extract of leaves; 500 mg/kg) were also reported. Significant increase in protein C, thrombin, antithrombin complex, and decrease in fibrinogen & levels of platelets aggregation were noted at high doses [31]. Xu J *et al* reported that the fruit has an activity of preventing obesity by modulating the gut microbiome in mice[32]. Angiogenesis, collagen deposition, andre epithelialization have been shown as contributing to wound healing activity of Jamun honey[33]. These in-vitro and in-vivo experiments with its details are summarized in table 1.[21-33]

Correlation of Therapeutic Activity and Pharmacodynamics of *E. jambolana*

Seeds, leaves and bark of *E jambolana* are commonly used for the health benefits. The plant is described having *guru, ruksha* (heavy and dry) properties, *kashay, madhur rasa* (astringent-sweet taste), *sheetaveerya* (cool potency) and *katuvipak* (after digestion pungent effects) leading to amelioration of *kapha-pitta doshas*. Its main sites of action are *raktadhatu* (blood), *mahasrotus* (gastrointestinal tract) and *pranvahasrotas* (respiratory system).

Kashayrasa, katuvipak and *rukshaguna* ameliorate aggravated and vitiated *kaphadosha* and at the same time reduce over hydration and increased looseness of adipose tissue. *Kashay rasa, sheetaveerya* reduce vitiated *pitta* thereby burning sensation and inflammatory changes. *Kashay rasa* is made up of Earth and Air elements; with *rukshaguna* it absorbs over secretions (*upashoshan*) such as wound secretion, increased urination (*Bahumutrata*) and bloody discharge (*raktastanbhan*). *Kashay rasa* and *rukshaguna* have capacity to hold the peristalsis there by reducing intestinal motility disorders (e.g. *Atisar/pravahika*) and gastric emptying-time additionally contributing to good digestion. This also correlates with the prevention or correction of gut dysbiosis. Its *pramehaghna* (antidiabetic) activity

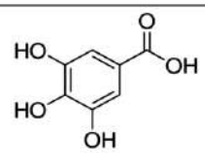
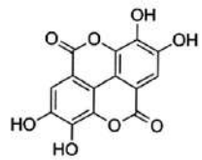
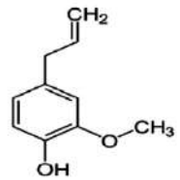
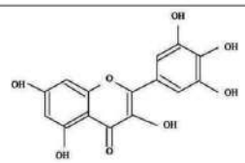
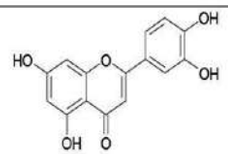
Table 1. Biological plausibility of the plant

Petroleum ether (PEE), CHCl3 (CE) , ethyl acetate (EAE) and methanol (ME)] and isolated compounds	Antioxidant	DPPH free radical scavenging H2O2 radicals methods	Sasikala M , 2016
Compound from leaves kaempferol-7-O-α-l-rhamnopyranoside	Anti-inflammatory	Lipopolysaccharide (LPS)-stimulated RAW 264.7 cells.	Jain A et al 2010
Aqueous extracts of seeds	Antidiabetic-hypoglycemic	Inhibition of carbohydrate hydrolyzing enzymes	*Ahmed, et al. 2009*
Ethanolic extract of fruit pulp hydroethanolic extract of leaf	Anti-dyslipidemic, ↓Hypertriglyceridemia	Diet induced hyperlipidemic rats, MSG induced obese rats	Bilal R. et al 2011, França LM, 2019
Pre-treatment of hydroalcoholic extract of fruit pulp for 30 days	Cardioprotective	Isoproterenol (ISP)-induced myocardial damage in rats	Shukla SK, 2014
Aqueous extract of fruit pulp	Nephroprotective	STZ induced DM rats	Behera S R,2014
Hydroalcoholic extract of leaves(0.5g/kg/day) ,orally, for 8 weeks	Antihypertensive	Spontaneously hypertensive Rats, normotensive Wistar rats	Ribeiro RM 2014
Purified compound- α-hydroxysuccinamic acid.	Anti -atherosclerotic	STZ induced diabetic rats; atherosclerotic diet: hyperglycemia-induced atherosclerosis	Tanwar RS, 2011
Methanolic extract of leaves (500 mg/kg)	Anti-coagulant / anti-platelet	Healthy white albino rabbits	Rehman AA 2019
Fruit extract for 8 weeks 100/mg/kg/ day orally	Antiobesity and liver steatosis	High-fat diet (HFD)-fed mice.16SrDNA nalyses.	Xu Jet al , 2019
Jamun honey	Wound healing	Diabetic mice	Chudhary A et al 2019

Table 2. Ayurvedic Dravyaguna rationale and Biological Plausibility of the plant

Plant Dravyaguna	Biological correlates
Madhumehahara	Antidiabetic
Mutrasangrahaneeya	Anti-polyuria
Vranajit	Wound healing
Veeryapushti& Balaprada	Reduction in testicular impairment, and apoptosis : Anabolic and anti-apoptotic?
Grahi /Atisarvinashini	antidiarrheal
Dahajit	coolant
krumidoshhantri	Anti-bacterial, antiviral, Anti-microbial
Shoshshamani	?diabetic thirst
Swaskaphakasavinashini	Protection from Bronchitis, asthma, cough Protective against respiratory infections?

Table 3: Structures and activities of major phytoconstituents

Phytoconstituents	Structure	Activity
Gallic acid 3,4,5-trihydroxybenzoic **acid** $C_6H_2(OH)_3COOH$		• Cardioprotective • Neuroprotective • Hyperglycemia, dyslipidemia • Oxidative stress • immuno- and thrombo-regulatory
Ellagic acid dilactone of hexahydroxydiphenic acid. $C_{14}H_6O_8$		• Antidiabetic, Antiglycation • Antidyslipidemic • Oxidative stress • decreases endothelial ROS levels and improves vascular relaxation • ↑C-peptide, glycogen and carbohydrate metabolic enzyme • inhibition of ERK1/2 and down regulation of NOX4
Eugenol 2-Methoxy-4-(prop-2-en-1-yl)phenol $C_{10}H_{12}O_2$		• Hypoglycemic,↓insulin resistance, Antiglycation • ↓oxidative stress • ↓ inflammation • ↓ α-glucosidase • ↓ oral biofilm prevents AGE formation by binding to ε-amine group on lysine, • GLUT4-AMPK signaling pathway
Jambosine alkaloid $C_{10}H_{15}O_3N$,		• ↓converting starch into sugar
Jamboline glycoside		↓converting starch into sugar

is seen through its *kaphapittaghna* properties.

The analogy between Ayurvedic *dravyaguna* rationale and these reported pharmacological actions or biological activity is explained in table 2.

Phytochemistry of *E. jambolana* Linn and Therapeutic Potential in Diabetes mellitus

The plant is a rich source of gallic acid, ellagic acids, anthocyanins, glucosides and flavonoids[34-38].

Roots contain jambosin, jambolin, stem contains phytoactives viz betulinic acid, β sitesteriol, eugenin, quercetin, gallic acid, ellagic acid. Leaves have phytoconstituents like quercetin, myricetin, tannin, galloyl carboxylase, glycosides, and flowers have reported to have kaemferol, quersetin, isoquercetin, eugenol, and triterpenoid. Seeds are good source of gallic acid, ellagic acid, saponins and triterpenoids. Fruits contain glucose, fructose, citric acid, gallic acid, anthocyannins, and good amount of calcium, Iron, Magnesium, Niacin (vit. B3), Phosphorus, Potassium, Riboflavin (vit. B2), Thiamine (vit. B1), Vitamin B6, Vitamin C etc. Some of the phytoconstituents are studied for their activity as stated in table 3.

Future Scope and Direction for Integrative Pharmacology

E. jambolana is used in traditional medical practice for diabetes since many decades though direct reference of it for the management of Prameha/ madhumeha is not available in Ayurvedic classical texts such as *Brihattrayi* (three major; Charak-samhita, Sushrut-Samhita and Ashtang-sangraha) and *Laghutrrayi* (three

minor; Madhav-nidan, Sharngdhar-Samhita and Bhavprakash). However, reference from *Nighantu Ratnakar*[39] (19th Century) throws light on antidiabetic activity of seeds of *E. jambolana*. Biological plausibility of various parts of the plant and their diverse extracts through preclinical and clinical pharmacology studies have demonstrated beneficial activity for diabetes and its complication which is reported since 1897[40].

Ayurvedic *Dravayaguna* (Ayurvedic pharmacology) rationale suggests *E. jambolana* seeds role in the management of *Prameha* (pre-diabetes), obesity (metabolic syndrome) and associated gastrointestinal diseases disturbing gut microbiome. However, *E. jambolana* seed powder wouldn't be recommended in *madhumeha* (diabetes) because of its *vata-dosha* aggravating and vitiating properties. *Madhumeha*, as it is known to be a *vata-dominant* disease. However, fruit of *E. jambolana* is advised in *Pathya* (recommended diet) because of its antidiabetic and nutritious properties[41].

Ayurveda is an experience-based intuitive knowledge system whereas current mainstream bio-medicine is experiments-based investigative evidence system. The former is driven by property-activity matrix of a substance whereas the latter is driven by structure-activity relationship of a substance. Convergence of experience-based and evidence-based knowledge systems has a potential scope to fructify into a futuristic integrative pharmacology. Efforts in development of phytopharmaceuticals[42] seems to be the rational path towards this direction.

Conclusions

Diabetes is known to cause inflammation and oxidant damage as important relevant features in pathogenesis. Anti-inflammatory and antioxidant properties reviewed presently indicate a strong biological plausibility for conducting detailed observational therapeutic studies for its anti-diabetic action.

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