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RESEARCH COMMENTARY

PHARMACOLOGY AND DRUG DISCOVERY

Pharmacological Efficacy of *Allium hookeri*, *Premna herbacea* and *Lysimachia candida* in Regulating Metabolic Dysfunctions

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1 Background

Diabetes mellitus is a chronic health disorder that can severely affect the functions of vital health-organs like kidney, heart, eyes, liver; and because of this, the other health disorders of diabetic patients make the treatment process complicated(1). A recent example is Covid-19 and the diabetic patients (mainly type 2 diabetic) with Covid-19 infection experienced comorbidity and suffered most(2). The future projection is that, by 2040 almost 8% of the total living human population will continue their life with type-2 diabetics(3). Unlike type-1 diabetics, in type-2 diabetes mellitus (T2DM) either the secretion of insulin from the pancreaticβ cells gets hampered or insulin comes to be resistant to the insulin-receptor (IR). The insulin resistance is manifested by different complex molecular mechanisms, mainly by mutation or abnormalities in the activity of several checkpoint proteins such as AKT, PI3K, mTOR, GSK-3β, JNK, AMPK, SIRT-1, GLUT-4, etc.(4). The imperative solution for the type-2 diabetics is to overcome the insulin resistance or increase the insulin production, but both the processes are continuous rather than repairable. Traditional knowledge system of North East Region (NER) India includes many herbs or medicinal plant products which have been shown to be effective in controlling the type-2 diabetics in several experiments and many researches are continuing to explore new plant materials in search of novel non-toxic and affordable compound(s) for better management of T2DM or associated complication and to overcome the drug resistant issue(5). North East India holds a rich biodiversity and is a popular source of different endemic medicinal plants(6). A majority of inhabitants of NER, India relies on traditional knowledge-based treatment to manage different health disorders including diabetics, blood pressure, heart disease, etc. As per claim of the traditional healers indigenous herbs are sometimes more effective than the modern medicine in the treatment of several diseases. This is the basis of interest of researchers for scientific validation of the traditional knowledge-based treatment option for different health issues. Elsewhere, many modern drugs have been developed/discovered enroute from traditional knowledge(7). Based on this rationale, a research project was executed to understand the potential role of three selected indigenous medicinal plants viz. *Allium hookeri*, *Premna herbacea* and *Lysimachia candida* from NER in management of metabolic disorders. Endemic medicinal plants are expected to be enriched with bioactive phytochemicals (mainly secondary metabolites) and their quantitative distribution in plants owing to specific weather conditions, soil physicochemistry and regional landscape(8). Several traditional healers of NER have been using these three plant materials in management of different metabolic disorders including T2DM.This commentary draws a summary of the previous research findings on scientific validation and to understanding the efficacy and prospect of those selected plant materials in management of T2DM, mainly through actions on insulin resistance.

2 *Allium hookeri* in T2DM management

Allium hookeri (AH) or hooker chive is an edible perennial herb from the Liliaceae family and endemic to South-East Asia. This plant material is commonly known as Piyanj/ Ponoru in Assam and Maroi napakpi in Manipur and the people of this region consume it through daily food mainly due to its diverse health benefits and characteristic aroma with three root tastes (sweet, bitter and hot). The plant

material is known for its high content of sulfur compounds known to have role in improving lipid metabolism and also effectiveness against hypertension, cancer, diabetics, and bacterial infections(9). Traditional knowledge of indigenous population of NEI and experiences of the local traditional healer suggests that the plant material is also effective against common coughs, colds, ulcer, wounds and burns, and as a potent cardioprotective material(10). There are only a few studies conducted, including our own, to understand the effectiveness of AH in T2DM management with underlying mechanisms and molecular distribution of bioactive secondary metabolites in these plant materials. Volatile organo-sulfur compounds like allicin and alkyl thiosulfinate from this plant parts are the major bioactive component and have already been proven for lowering blood glucose level and adipogenesis in diabetic models(10; 11). Allicin is a highly unstable compound and converted to various other oil-soluble bioactiveorgano-sulfur most likely diallyl sulfide (DAS), diallyl disulfide (DADS) and diallyl trisulfide (DATS) (10; 11). Those sulfide compounds have been thoroughly investigated against different cancers including breast, prostate, etc. and found to be very potent(12). A group of researchers showed that the water extract of AH root is able to increase the GLUT-4 expression to further enhance the glucose uptake in adipocytes(10). In another study, it has been shown that water extract of AH roots was effective in protecting the damage of pancreatic β-cells in streptozotocin induced diabetic rats. The mechanistic effect was identified through ability of the through reduction of the over expression of NF-Bp65 and NF-Bp65-inducedinflammatory cytokines (IL-6 and TNF-α) (9). (13) have shown that the ethanol extract of AH root was more efficacious to reduce the blood glucose level in C57BL/J-db/db mice(13). The work from our group confirmed that the alcoholic extract of AH leaf was able to stimulate the glutathione biosynthesis to restore the glutathione level and to regulate the blood glucose level(11). Overall, the data generated so far from different studies are promising and indicate that AH extracts can act as an important functional food to prevent the occurrence of diabetic related symptoms without any detectable toxicity. The established mechanistic insight of AH mediated modulation of glucose metabolism is through regulating the fasting blood glucose, glucose tolerance, and insulin activity.

3 *Premna herbacea* in T2DM management

Premna herbacea (PH) Roxb, another perennial herb, belongs to Lamiaceae family, locally known as Mati-galdabin or Mati-feurain in Assam, India, used by the local healer from the Bodo community to treat many health disorders including diabetics(14). Different plant parts of PH are reported to have diverse activities and used to manage different health disorders. For example, the rhizome of PH is known to have anticancer activity, the leaves or roots of PH are used to treat headache, rheumatic pain, cough, fever, cold, ulcers, rheumatism, gout, sprain, asthma, cholera, etc.(15). The therapeutic potential of this plant is also documented in Indian Ayurveda, and the local population used to consume this plant materials from ancient time as a vegetable for known traditional health benefits. In search of bioactive phytochemicals for the management of diabetics, three major bioactive compounds have been isolated from the root of this plant materials viz. 1-Benzoyloxy-8-tetradecanoyloxy-geranilane, 1-Benzoyloxy-8-(octadec-9-enoyl) geranilane, and 1-Benzoyloxy-8-octadecanoyloxy-geranilane among which the second one is established as the most potent to reduce the blood sugar level(16). An icetexane was isolated from the root of PH and showed antifungal and anti-microbial activity(16; 17). We used leaf biomass of PH in our own study to investigate its antidiabetic effect specifically addmiring IR.The methanolic extract of the leaves of PH was able to enhance the glucose uptake in high fat-high fructose induced diabetic rats(14). Furthermore bioactivity guided fractionation confirmed the presence of a major bioactive compound isoverboscoside, which was found to be potent to reduce the blood glucose through synergizing the JNK and AKT/mTOR signaling. The detailed phytochemical portfolio of different Premna species is collectively presented by Dianita and Jantan in 2017(15). Although they have identified more than 250 secondary metabolites with diverse activity through different *In vitro* and *In vivo* experiments, the molecular signature of PH is yet to be explored.

4 *Lysimachia candida* in T2DM management

Lysmachia candida (LC) Lindl, locally know as Loosestrife in Assam and Kengoi in Manipur, form *Primulaceae* family, is known for diverse medicinal values which helps to recover from swelling, bone fracture, and dermatitis and also acts as an antipyretic herb(18). Although documentation on distribution of bioactive molecules (mainly secondary metabolites) from the species is available, there is very little information on this ecotype of LC. For example, Lysimanoside, Lysikokianoside, Anagallisin C, and Astragalin are the few among the potential bioactive components isolated from this ecotype of LC prevalent in China. We confirmed for the first time that the isolation of bioactives from the ecotype of LC, present in the Manipur state of NEI(19). Several other triterpenoids, saponins, and flavonoids of this ecotype have also been characterized and their potent biological activity such as cardioprotective, anticancer, anti-inflammatory, were investigated(19).

(18) showed that the whole plant methanolic extract of LC is able to prevent the fatty liver in high-fat high-fructose (HFHF) induced rats(18). The results of our research have shown that the methanolic extract of the ecotype is able to reduce the insulin resistance in HFHF-induced rats. Obesity is another complex metabolic disorder and insulin resistance in T2DM is associated with obesity and related complications. We also showed that the methanolic extract of LC and a major bioactive compound Astragaline was able to reduce the obesity (body weight and free fatty acids) of HFHF induced rats through substantial changes in plasma leptin level(19).

5 Conclusion

Allium hookeri (AH) confirmed to have the potential efficacy for management of T2DM, obesity, and related complications. The anti diabetic/anti obesity effect of methanolic extract and different solvent fractions of these selected plant materials on different established models indicated the pres-

Table 1: Summary of bioactivities in both *In vitro* and *In vivo* models of the selected plant materials

Name of the Plant	**Fraction /Extract**	**Bioactive Molecule identified**	**Bioactivity**				**References**
Allium hookeri	Water extract (root)	-	*In vitro* Model	Findings (*In vitro*)	*In vivo* Model	Findings (*In vivo*)	(10)
	Water extract (root)	-	3T3-L1 cells	increase GLUT-4 expression	-	-	
	Water extract (root)	-	-	-	STZ-induced diabetic rats	loss of body weight	(9)
			-	-		increased pancreatic weight	
			-	-		protecting the damage of pancreatic β-cells	
	Ethanol extract (root)	-	-	-	C57BL/J-db /db Mice	reduce the blood glucose level	(13)
						reduce the plasma leptin level	
	Methanolic extract(shoot)	-	L6 cell line	increase in GSH level	Sprague Dawley rats	stimulate the glutathione biosynthesis	(11)
				decreased GSSG level		restore the glutathione level	
				an increase in GSH/GSSG ratio		regulate the blood glucose level	
Premna herbacea	Methanolic extract(leaf)	Isoverbascoside	L6 cell line	stimulation of JNK and AKT/mTOR signaling cascade	High fat-high fructose induced diabetic rats	enhance the glucose uptake	(14)
Lysimachia candida	Methanolic extract(leaf)	-	-	-	High fat-high fructose induced diabetic rats	prevent the fatty liver	(18)
						reduction of body weight	
	Methanolic extract (leaf)	Astragaline	3T3-L1	inhibit chemically induced differentiation in 3T3-L1 preadipocytes without any cytotoxicity	High fat-high fructose induced diabetic rats	reduce the insulin resistance	(19)
						reduces the body weight and free fatty acids	
						substantial changes in plasma leptin level	

ence of different plant bioactives Table 1. The identified bioactives were associated with the observed effect in terms of reduction of blood glucose, body weight, and fatty acids Table 1. The mechanism of action of extract and bioactives in T2DM were established. Overall, regular consumption of these plant parts by the local people in their daily diet based on their experience on diverse health benefits without notable toxicity actually boost their immunity. Thus these plants may be considered as an important ingredient for the development of functional food based on the proof obtained on scientific validity of the traditional knowledge.

Conflict of Interest

The authors declare no conflict of interest in this reported communication.

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