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A Review on Futuristic Scope of Agents Related to Amphibian's Skin and Plants-based Sources in Type 2 Antidiabetic Therapies

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Abstract

Based on the current scenario type-2 diabetes has been labelled as one of the major health issues, approaching exponentially towards mind boggling stage of epidemic globally. Considering to its lifelong latency from early to old ages, less awareness to its particular genotype and phenotype and hefty cost involved in its management and treatment; there is substantial need for more advance, personalised and economical therapeutic approaches for its effective therapy and treatment. The current review here discusses peculiar agents from amphibian's skin and rarely explored distinctive plant sources with potential to be a viable therapeutic option for type-2 diabetes, therefore, could be devised into effective future treatment strategy to it and also to its related microvascular and macrovascular complications. Based on the literature search the therapeutic scope of agents from amphibian's skin and selected plants sources are delineated, sighting their activities and prospects as to be future revolutionary remedy to type-2 diabetes and associated hitches such as their insulin releasing ability in pancreatic beta cell lines and primary islets cells, effects on glucose level and on other metabolic parameters such as obesity, lipid profile and pancreatic beta cell function etc.

Keywords: Type-2 diabetes, Distinctive plant sources, Metabolic parameters, Glucose level, Peculiar agents and amphibian's skin.

INTRODUCTION

Type 2 diabetes also refer as to noninsulin dependent diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia as result of insufficient insulin secretion by pancreatic beta cells/inability of tissues to respond to biological action of released insulin or both. This prolonged, elevated glucose level further observed to add up multiple microvascular and macrovascular complications in type 2 diabetes patients.^[1,2]

The prevalence of diabetes around the world is increasing exponentially despite of rigorous research and discovery multiple antidiabetic agents both conventional and non-conventional. As per recent stats, number of individuals affected with diabetes in 1980 rose from 108 million to 422 million in year 2014 globally and are expected to rise to 642 million by 2040. Moreover, diabetes being a major cause to diseases like heart attack, blindness, kidney failure etc has been directly associated to 1.6 million deaths and 2.2 million deaths were recorded due to its major complications such as rise in glucose level in year 2015.

In specific to UK, in year 2019 almost 4.7 million of people has been diagnosed with diabetes i.e. 1 in every 10 individual and the number of people are thought to ascend to 5.5 million by 2030(6% of UK population). Similarly, in country like India a developing nation hold one of the largest diabetic population of 69 million and by 2030, these Figures are estimated to grow up to 109 million, thus, projecting diabetes as the global health issue and a major burden to number of countries economies.^[3-6]

Considering such staggering incidence rates and limitations concerning to currently available antidiabetic agents, there is an urgent need to more economical and novel treatment strategies with minimal side effects. Therefore, owing to the vast applications and important sources from nature in the field of medical sciences, developing bio prospected amphibian skin and plant based bioactive compounds might turn to novel method devising a therapeutically effective treatment options for type 2 diabetes and possibility of creating steadfast health care solutions in the respected field.^[7-12]

At present, evidence suggest both amphibians' skin/plant-based treatments could be adopted as future frontline approaches to diabetes therapy. Research shows that peptides from variety of frog skin sources hold immense potential to be developed into anti diabetic agents. Host defense peptides and their derived analogues from amphibian sources like Esculentin-2Cha,^[13-16] Tigerinin-1R,^[17-20] PGLa-AM1,^[11,21] Hymenochirin-1b,^[22-24] Brevinin,^[25-27] Magainin-AM2,^[28,29] Xenopsin,^[30-32] Careulein,^[33] Temporin,^[34] Alyteserin,^[35] Gaegurin-6,^[36] CPF-SE1,^[37] etc. has been observed to exhibit overwhelming insulinotropic/ Glucoregulatory effects via improving beta/islet cell function, glucose tolerance/homeostasis, *in vitro* stimulation to insulin release/sensitivity, glycaemic control and secretion of glucagon-like peptide 1 (GLP-1) in high fed obese animal models. Moreover, they have also been witnessed to cause significant reduction to pancreatic insulin, plasma glucagon concentrations and total body fat and plasma triglyceride levels.

Similarly, extracts/agents from multiple plant species like *Humulus lupulus*,^[38] *Medicago sativa*,^[39-41] *Agrimony eupatoria*,^[42] *Ocimum sanctum*,^[43,44] *Cinnamomum*

zeylanicum,^[45-47] *Terminalia bellirica*,^[48] *Asparagus racemosus*,^[49] *Terminalia chebula*,^[50,51] *Asparagus adscendens*,^[52,53] *Curcuma longa*,^[54,55] *Swertia chirayita*,^[56] *Trigonella foenum-graecum*,^[57,58] etc also carry's prospects to be developed into vital anti diabetic agents. Additionally, the drug Metformin widely used in modern era in diabetes is also derived from plant *Galega officinalis*.^[59]

However, decades of research on variety of such amphibian's skin/plants-based agents none of the steadfast and economical solutions has been achieved till date countering type 2 form of diabetes and its related complications. Based on this fact the current review here aims to discuss unique and less widely explored agents from natural sources like insulinotropic peptides isolated from frog skin secretions belonging to class Pipidae and agents from marine/local plants (*Laguncularia racemosa*, *Pterocarpus marsupium* and *Cymodocea nodosa*) bearing immense potential to be transformed into vital futuristic therapy against type-2 Diabetes.

The profiling of the agents will be done based on their past and current research abilities against diabetes and related complications such as their insulin releasing ability in cell lines like BRIN-BD11 beta pancreatic cell lines (*in vitro*) and also in obese diabetic animal models (*in vivo*) concerning to their potency to regulate glucose-tolerance and facilitating insulin-release etc.

Frog Skin Based Peptides

In the search of viable and steadfast effective health solutions against serious diseases and infections in the field of medical sciences, host defense peptides isolated from frog skin could be major breakthrough laying down effective future therapeutic options. There have been number of proofs suggesting peptides isolated from frog skin showing diverse therapeutic abilities such as cytolytic activities against variety of bacteria and fungi, as to their designated activity to function as host defense peptides against pathogenic microbes.^[60-63] Moreover, evidences propose that the isolated peptides also holds potential to be an vital anticancer/antitumor,^[64-67] antiviral,^[68-70] immunomodulatory,^[71,72] agents etc.^[10]

Similarly, regarding effective antidiabetic activities, peptide isolated from Pipidae family frogs hold immense ability to be developed into as conventional diabetic therapy.

Members belonging to Pipidae family also known as to be the clawed frogs, identified with their dorsoventral flattened body. They are further divided mainly into four genera based on their geographical existence. The very first South American native Pipa while the other four *Pseudhymenochirus*, *Xenopus*, *Hymenochirus*, *Silurana* are found in sub-Saharan Africa. Moreover, having taxonomically dubious evolutionary history, some frogs of the family such as *Silurana* and *Xenopus* are also subclassed in Xenopodinae family.^[11,73-76]

Insulinotropic peptides from Pipidae family

The skin secretion from this frog family contains multiple numbers of peptides out of which few have shown prospects to developed into antidiabetic agents.

Peptides from *Xenopus amieti*: The skin secretions from *Xenopus amieti* an octoploid volcano clawed frog carry's diverse range of peptides:

Magainin (AM1 and AM2): Based on the immense potential, both Magainin AM1 and Magainin AM2 have been observed with antidiabetic activities at both *in-vitro* (clonal BRINB11 β -cells) and *in-vivo* (mouse islets) levels. Magainin-AM1 at ≥ 100 nM concentration has been witnessed to show

nontoxic concentration dependent facilitation of insulin release in clonal BRINB11 β -cells cell lines and isolated mouse islets. However, Magainin-AM2 was found to be more potent to stimulate insulin release from clonal BRINB11 β -cells cell lines and in mouse islets along with improving glucose tolerance and consistent reduction in non-fasting blood glucose level and upregulation of non-fasting plasma insulin concentration thus, maintaining glucose homeostatis and beta cell function in high fed obese mice. Moreover, they have also been found to stimulate rate of release of glucagon like peptides (GLP-1) and incretin peptides in murine enteroendocrine GLUTag cell lines at non pernicious concentrations to cells and were also significantly able to induce membrane depolarization and intracellular Calcium (Ca^{2+}) in BRIN-BD11 cell lines.^[11,28,77]

Similarly other peptides from *Xenopus amieti* like PGLa-AM1, Xenopsin-precursor fragment (XPF-AM1), Caerulein precursor Fragments (CPF-AM1, AM2, AM3 and AM4) had also shown decisive action to produce significant induction of insulin release in BRIN-BD11 cell lines, mouse islets and human based pancreatic β -cell lines 1.1 B4 at appropriate concentration without any toxicity to the cells.^[77]

Peptides from *Hymenochirus boettgeri*: The skin secretions from *Hymenochirus boettgeri* an Congo dwarf clawed frog contains peptides with almost similar structures known as to be hymenochyrins,^[78,79] out of which Hymenochirin-1B(a cationic, amphipathic, α -helical peptide) and its related analogues has been observed with the ability to increase the rate of concentration dependent insulin in BRIN-BD11 cells with no cell toxicity at adequate concentration and in mouse islets. The related peptides [P5K] and [D9K], based on their structural activities displayed maximum insulin release rate in mouse islets which was more than to its native peptide. Additionally, there, intraperitoneal administration to high fed obese mice has resulted into improved glucose tolerance along with the up regulated insulin secretions.^[22-23,77] Moreover, peptides from this frog skin secretion have also been witnessed to show immunomodulatory, antibacterial, anti-tumor activities.^[80,81]

Peptide from *Pseudhymenochirus merlini*: *Pseudhymenochirus merlini* also known as to be Merlin's clawed frog, their skin secretions similar to other pipidae frogs in the family carry's number of cationic, α -helical host-defense peptides like Pseudhymenochirin-1 Pa and -1Pb almost resembling to each other except by one amino acid as well as hymenochirin peptide,^[82] while the other peptide pseudhymenochirin-2 Pa peptide doesn't resemble to any of the peptide in the family pipidae. It has been witnessed that pseudhymenochirin-1Pb and pseudhymenochirin-2 Pa both the peptides were able to induce insulin release in BRINBD11 clonal beta cells at certain concentrations. Additionally analogues [R8r] of pseudhymenochirin-1Pb also found to potentiate insulin release with low hemolytic activity. Additionally, along with insulinotropic activities the peptides from this frog were also been found to show effective antimicrobial activity with broad spectrum along with antitumor activity in mammalian cells.^[24,77]

Plant based agents with medicinal properties

There have been numbers of plant-based agents that has been utilized to elicit medicinal responses to variety of diseases including those whose etiology and occurrence is still needed to be addressed immensely. Plant based agents such as Curcumin, Resveratrol, Epigallocatechin-3-gallate (EGCG) etc,^[83-85] has been witnessed to show anticancer ability while there are several other plant agents with variety of medicinal activities like antimicrobial,^[86,87] antiviral,^[88,89] and antidepressant,^[90,91] antioxidant activities, antitumor, antifungal etc.^[92,93] However, keeping in mind the multi-application use of plant based agents

none of the permanent solution has been achieved till date especially to those diseases which are still conundrum for the researcher around the world like HIV, Cancer, and Diabetes etc.

Therefore, to achieve steadfast solutions for diseases like diabetes exploring unique plant sources and related agents which has not been studied or little has been discovered about their biological activity could be novel way for achieving therapeutic advancement in drug therapy.

Antidiabetic/Insulinotropic activity of prospected plant-based agents

As to device futuristic antidiabetic drugs the review here explores the biological activity of unique marine plant *Laguncularia racemosa* along with *Pterocarpus marsupium* and their possibility to be developed into advance antidiabetic therapy. The profiling to their prospects to be developed as antidiabetic/insulinotropic agent is done based on their previous biological and antidiabetic-activity if any.

***Laguncularia racemosa*:** Being unique and less widely explored marine plant *Laguncularia racemosa* is rarely been reported for its antidiabetic activity. However, its hydroalcoholic and methanolic extracts has been witnessed to show enzymatic activity and thrombin-induced plasma coagulation.^[94] Moreover, the ethyl-acetate extracts of endophytic-fungi strains obtained from their leaves has shown potent antimicrobial-activities towards. bacteria like *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* etc.in addition to its phenolic. compound integracin with protein. kinase inhibitory activity in suppression of variety of human tumour.^[95-97]

***Pterocarpus marsupium*:** The Phenolic/aqueous extract from the leaves/roots of *Pterocarpus marsupium* has shown to be capable of managing hyperglycemia, hyperlipidemia and major diabetes related-complications through reduction of fasting blood-glucose level, glycosylated haemoglobin levels and facilitating the serum insulin and glycogen-contents to skeletal&hepatic-muscle.in diabetic-rats.^[98-104] While its crude and stem bark extracts were also found to possess anti hyperglycaemic activity with ability to lower elevated glucose in animal-models.^[105,107] Moreover, the methanolic/aqueous extract of stem bark.

***Cymodocea nodosa*:** Similar to *Laguncularia racemosa*, *Cymodocea nodosa* is also a Marine plant, which has been not been so much explored in regards to its biological activities. However, it extracts in recent research has shown to be a very effective in diabetes treatment and its related complications. The extracts from plant have been observed to inhibit vital hypoglycaemia inducing enzyme and α -amylase activity, shielding the pancreatic beta cells and its function thus, decreasing glucose level in blood and regulating lipid levels in alloxan-induced diabetic rat. Moreover, the extract has also shown to reduce the body weight while inhibiting the lipase activity in obese high fed rats leading to decreased triglycerides levels, low density lipoproteins (LDL), total cholesterol level and rise in high density lipoprotein cholesterol (HDL) and maintaining blood lipid homeostasis.^[108-110]

CONCLUSION

The scope of bioactive peptides/agents from unique natural sources such as rare species of plants or amphibian's skins sources as enduring therapeutic option for diabetes is very much of interest and new direction for researchers around the world in terms to their distinctive attributes and functional features. Considering the fact based on the limitations to currently available conventional diabetes medications there is a stern and immediate need to explore such novel agents/peptides that has rarely been studied for their

biological activity and therefore could be potentially devised into a futuristic anti diabetic therapy. Diabetes based on its long latency, which not only have negative health effects on patients but also have consistent mental and financial impact. As also being common, with staggering number of increasing incidence rates around the world diabetes is an ideal choice for research and is also comparatively easy to monitor as other diseases. The Preliminary data presented in the review shows the substantial prospective for the peptides/agents and their potential activity against diabetes and its related complications. However, such interventions through rare biological source of means could be time consuming and require multiple phases of clinical study done meticulously before can be recommended to as useful anti diabetic treatment strategies for patients. Thus, a confirmational activity for peptides/agents along with their optimal doses, usage, administration profiling etc are very much desirable through a well-designed clinical trial.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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