Therapeutic innovations for type 2 diabetes: if Nature is the solution?

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Summary

There are nearly 9 million eukaryotic and prokaryotic species on earth, living in a wide variety of conditions ranging from thermal fissures to cold arctic environments. Anticancer, antiviral, antifungal drugs and antibiotics, are still directly extracted from many species or reproduced with improvements by chemical synthesis as biomimetics. GLP-1 analogues and metformin, respectively derived from the saliva of a venomous lizard of the *Helodermatidae* family and from the medicinal plant Galega Officinalis, are currently used as therapeutic drugs of type 2 diabetes worldwide. Therefore, the knowledge of terrestrial plants, animal species such as amphibians and reptiles, and aquatic biodiversity such as sponges and algae, may pave the way for the discovery of new insulin-secretagogues and insulin-sensitizers.

Key Words: Diabetes; insulin secretors; insulin sensitizers; pancreatic beta cell.

1-Introduction

Human has always been inspired by plants and animals for healthcare, as cited by Hippocrate "*Nature itself is the best physician*". Plants have been able to offer medicines such as analgesics (morphine and codeine), anti-cancer drugs (taxol), antimalarials (artemisinin) or aspirin. Other analgesics (Prialt of the sea cone), many vaccines (hepatitis A, influenza), inflammation modulators and many anti-venom drugs are from the animal world origin. The drug discovery has been accelerated and fostered by the domestication of animals. For example, insulin has been discovered thanks to pancreatectomized dogs as animal model of diabetes. This animal model has enabled Sir Frederik Banting to reveal the therapeutic activity of insulin, and thus to treat the first diabetic patient [1]. Before the development of genetic engineering, insulin from beef and pig was used to treat millions of patients. Metformin is the insulin sensitizer drug that is currently the most prescribed antidiabetic medicine worldwide for type 2 diabetes (T2D). The insulin sensitizing effect of Metformin has been first described in the Middle Age with the use of the G*alega officinalis*, also known as "French lilac" plant. Glucagon-like peptide 1 (GLP-1) mimetics are a class of insulin secretagogues [2]. They have been originally discovered by an American team through the search for molecules from arthropod and reptile venoms that activate g-protein coupled receptors involved in the pancreatic amylase secretion. The most potent molecule has been issued from the venom of the Gila monster (*Heloderma suspectum*), in which resides the GLP-1 receptor agonist, exendin 4 [3, 4]. The half-life of the latter has been extended by chemical modification, leading to exenatide, an insulin secretagogue effective in the treatment of diabetes. These discoveries clearly demonstrate that anti-diabetic molecules can be found in biodiversity.

Although these insulin-sensitizing and insulin-secreting antidiabetic drugs are efficient for improving glycemic control in short and medium terms, their efficacy is reduced overtime. In addition, some of them cause digestive adverse effects and cannot be prescribed to some patients. For several patients, this loss of efficacy leads, quite rapidly, to the progression of the disease towards complications including cardiovascular, neuropathy, retinopathy, nephropathy, disabilities and blindness. As the consequence, insulin therapy is the only therapeutic option with its discomfortable use that will impact the patient's quality of life [5]. Finally, the therapeutic options when oral antidiabetic drugs fail are weak. Therefore, there is an urgent need in developing insulin sensitizers and secretagogues with long duration efficiency. With approximately 8.7 million plant and animal species worldwide including 6.5 million species living on earth and 2.2 million in the seas [6], it is highly possible to find out new antidiabetic drugs. This hope is supported, in this review, which presents some of the emerging and current active substances of marine plant and animal origins as future potential antidiabetics.

2- Antidiabetic drugs from the animal world

2.1. New GLP-1 analogues in the venoms of short-beaked echidna and platypus. The discovery of exendin

4 in the venomous saliva of the Gila monster has opened up new avenues of research for analogues from other animal species. Currently, some efforts are now being made to search for analogues with more selective therapeutic effects than those of exendin 4 and native GLP-1. In particular, GLP-1 analogues, also called GLP-1 receptor biased agonists (GLP-1RBA), are expected to be the future drugs of this class. While the GLP-1RBA acts at the same GLP-1 receptor, it can selectively target specific signalling pathways and thereby improve the durability of the effect on insulin secretion [7]. Two GLP-1RBA have been discovered in venoms of platypus (*Ornithorhynchus anatinus*) and in short-beaked echidna (*Tachyglossus aculeatus*), two mammals of the monotreme order living in Australia and New Guinea [8]. The two GLP-1RBA are structurally analogous to exendin 4, although they differ by 12 amino acids in their sequence. The affinity of both peptides for the human GLP-1 receptor is lower than native GLP-1. Nonetheless, these novel analogues stimulate insulin secretion in response to glucose through the preferential activation of one of the MAPK signalling pathways. In addition, both peptides are more resistant to digestion by dipeptidyl peptidase-4 (DPP-4) than exendin-4, thus confirming the hope for the development of new GLP-1 analogues with longer-lasting and more specific effects.

2.2. New ion channels modulators in the venoms of spiders, wasps, reptiles and amphibians

Venom toxins, as illustrated by exendin 4, are potential sources of receptor ligands that can lead to antidiabetic drugs. It should also be noted that a large number of toxins are ion channel modulators that can inhibit or activate metabolic enzymes. Some of these peptides are now drugs, such as Captopril, an angiotensin converting enzyme inhibitor, which is derived from the venom of the Bothrops jararaca viper ([9]. Captopril is prescribed for the treatment of hypertension and heart failure [10]. Peptides capable of modulating the activity of ion channels regulating insulin secretion have been identified so far. For example, Tigerinin-1R, a peptide derived from the skin of frog (*Hoplobatrachus tigerinus*), blocks the ATP-dependent potassium channel (KATP) and thereby stimulates insulin secretion, reproducing the antidiabetic class of sulfonylureas [11]. Tigerinin-1R is considered as a serious anti-diabetic candidate, as revealed in a preclinical study [12]. Similarly, Mastoparan, a peptide isolated from the wasp (*Vespula lewisii*), blocks the KATP in a mechanism involving GTP and stimulates insulin secretion in response to glucose [13]. However, the usage of this peptide as KATP inhibitor will experience the same drawbacks as sulfonylureas and glinides. Indeed, KATP inhibitors stimulate insulin secretion in the absence of glucose, which could lead to hypoglycaemia. To avoid this concern and to provide a true advantage to existing drugs, there is a need that future antidiabetics stimulate insulin secretion only in response to glucose stimulation. Toward this perspective, the calcium-activated high conductance potassium channels (KC) and voltage-dependent potassium channels (KV) are two possible candidates. KC and KV are two channels that repolarize the beta-cell membrane upon glucose stimulation. In fact, these two channels only act in the presence of glucose. Therefore, inhibition of these channels by inhibitors would maintain the beta cell in a depolarized state, which would prolong insulin secretion only in the presence of glucose. Preclinical researches report some KC and KV blocking peptides from the venoms of the striated cone, tarantula and scorpion as potential insulin

secretagogues (**Table 1**). Future studies will focus on the validation of the use of these inhibitors in clinical trials.

2.3. A new class of insulin-secretor in the frog's skin?

Several insulin secretagogue peptides, derived from the skin of amphibians belonging to *Pipidae* and *Ranidae* families, have been identified as potential anti-diabetic drugs [11]. This is the case for the Brevinin-2-related peptide (B2RP), a peptide of the northern frog (*Lithobates septentrionalis*), the Alyteserin-2a of the midwife toad (*Alytes obstetricans*), the Hymenochirin-1b of the African dwarf frog (*Hymenochirus boettgeri*), the Magainin-AM1 and AM2 of the *xenopus amieti* and the Esculentin-2Cha of the Chiricahua leopard frog (*Lithobates chiricahuensis*). All these peptides stimulate insulin secretion in mechanisms that do not involve KATP. The peptides enter the cells, depolarize beta-cell membrane and stimulate insulin secretion [14]. These peptides could pave the way for the development of a new class of antidiabetic drugs, although they may lead to hypoglycaemia.

2.4. An insulin analogue found in the marine cone

Insulin analogues, with fast or slow onset of action, are currently produced for better managing glycaemic control. The search for insulin analogues with improved pharmacokinetics and reduced risks of hypoglycaemia, remains a challenge. The discovery of an insulin analogue in the venom of the sea cone (*Conus geographus*), which is one of the deadliest marine snails for humans, is a promising sign in this quest [15, 16]. The insulin in the venom is thought to allow the sea cone to rapidly induce an insulin shock (dangerous hypoglycaemia) to its prey (fish) and its predators. Unlike human insulin, the insulin in the cone (INS-Co) is monomeric, lacking the B-chain that activates the insulin receptor. Despite of this missing structure, INS-Co is capable of activating the human insulin receptor and the downstream signalling. The presence of two tyrosine residues, located in the A chain of INS-Co, would explain the agonism of this atypical insulin for the human insulin receptor [15, 16]. However, the clinical use of this insulin is compromised due to its immunogenicity. Nevertheless, interaction studies between INS-Co and the human insulin receptor may contribute to the design of a new class of rapid-acting insulin analogues for the treatment of diabetes.

3- Medicinal plants for diabetes

3.1. Active substances in aromatic herbs against insulin resistance

Plants have been offering medicines for thousands of years. They are still used as traditional medicines in many countries in Africa, Middle East and Asia. The WHO lists almost 21,000 plants used for medicinal purposes worldwide, of which a great diversity is found in India [17]. Some aromatic plants, such as onion and fenugreek, have hypoglycaemic effects, as shown in preclinical and clinical studies. Daily ingestion of small slices of onions (100g/day) significantly reduces fasting and induces blood glucose levels in patients with type 1 diabetes and

T2D [18]. Onions appear to have antidiabetic activity regardless of the form in which they are administered, extracts [19], juice [20], lyophilized powder [21] or essential oil [22]. The numerous studies, carried out in rodents, report multiple pharmacological actions through which the onion would exert its antidiabetic activity. With its flavonoids such as quercetin and rutin, onion could inhibit intestinal glucose absorption by inhibiting α-glucosidase [23] and improve insulin sensitivity by stimulating GLUT-4 translocation, glucose absorption and insulin signalling [24].

Onion (400 mg/day) also has an important antioxidant activity. With its L-cysteine sulfoxides and allyl and propyl disulphides, onions could directly trap free radicals, one of the probable causes of insulin resistance and loss of insulin secretion [25]. Another medicinal plant, used as a food and herb, that improves insulin sensitivity is fenugreek (*Trigonella foenum-graecum L*). Fenugreek was originally used on the shores of the Mediterranean as a fodder plant in ancient times, hence its name (Greek hay). The seeds were later used in traditional medicine and cooking. Like Galega, which later gave birth to Metformin, fenugreek has been traditionally known since the Middle Ages for its orexigenic and hypoglycaemic effects [26]. A meta-analysis carried out on a dozen clinical studies confirms the efficacy of fenugreek in reducing fasting blood glucose and glycated haemoglobin when ingested at doses between 2 and 100 grams/day for several weeks as a dietary supplement [27]. This hypoglycaemic effect of fenugreek, widely confirmed in diabetic rodent models, has been associated with improved insulin sensitivity in a small group of patients with T2D [28]. In addition, when co-administered with a sulfonylurea in patients with T2D, fasting plasma glucose, post-meal plasma glucose and glycated haemoglobin were significantly improved compared to patients who received only the sulfonylurea without fenugreek [29]. In addition to trigonelline and diosgenin, fenugreek seeds contain polyphenols, including flavonoids. Moreover, fenugreek contains a special amino acid, 4-hydroxyisoleucine (4-HIL), which improves the glucose utilization and uptake in the liver [30].

3.2. Insulin-sensitizing flavonoids of herbaceous plants

Flavonoids form a subclass of polyphenols, grouped into flavonols, flavones, flavan-3-ols, anthocyanidins, flavanones, and isoflavones. The flavonoids provide the colours to most flowers, fruits, green tea and herbaceous plants of the Asteraceae family. Several *in vitro* and preclinical studies have shown that flavonoids, in particular flavones (e.g. tangeretine and wogonin), flavonols (e.g. quercetin) and isoflavones (e.g. genistein), improve insulin sensitivity. They also have antioxidant and anti-inflammatory activity in insulin-resistant adipocytes and hepatocytes. This effect of flavonoids is believed to be due to their anti-inflammatory effects in triggering some key players such as NF-κb and PPAR transcription factors. The antioxidant and anti-inflammatory effects of "purified" flavonoids have been observed in clinical trials in patients with T2D who have ingested some extracts of herbaceous plants such as wild chicory (*Cichorium intybus*), or sweet grass (*Stevia rebaudiana*) [31] or Milk Thistle (*Silybum marianum*) [32], containing more than 5% flavonoids. The black cumin (*Nigella Sativa*) is an annual herbaceous plant belonging to the *Ranunculaceae* family, which is enriched in

polyphenols including flavonoids [33]. The plant is widely grown in the Mediterranean countries, Middle East, Eastern Europe and Western Asia [34]. The black cumin is used as a spice in bread, yogurt, pickles, sauces and salads. Oral administration of capsules containing 2 grams of the black cumin for 3 months leads to significant reductions in fasting and postprandial glycemia, HbA1 and insulin resistance without significant change in body weight [35]. In a randomized, double-blind, placebo-controlled clinical trial, it has been shown that the 2 grams/ day ingestion of black cumin for 3 months improves the blood lipid profile and prevents the risk for cardiovascular disease [36]. Currently, N. sativa is increasingly being used as a therapeutic strategy for diabetes management [37]. It should also be noted, that flavonoids are present in other plants, such as lemon balm and cultivated flax (**Table 2**). In the plant extracts, flavonoids often coexist with fatty acids such as omega-3, hydrocarbons and other polyphenols, which also have effects on insulin sensitivity. Further clinical studies, and a more detailed characterization of all these extracts, have yet to be undertaken, to determine among them, the best antidiabetic active ingredient.

3.3. Spices for treating diabetes?

Cinnamon is one of the well-described spices with medicinal benefits, as already mentioned by Avicenna (980-1037) in "the canon of medicine" [38]. Cinnamon (*Cinnamomum verum)*, originating from the Ceylon cinnamon tree, has several medical properties including anti-inflammatory, antimicrobial and a preventive effect on the risk of colon cancer. In addition, cinnamon also has hypoglycaemic effect and thus antidiabetic activity. Cinnamon may even improve the effect of drugs and diet regimens on fasting blood sugar, HbA1c, triglycerides and total cholesterol levels, when taken as a dietary supplement [39]. Unfortunately, due to the heterogeneity of protocols and the origin of cinnamon, meta-analysis studies did not confirm this anti-diabetic effect of cinnamon yet. Sometimes, conflicting results have been published and particularly when cinnamon is extracted from *Cinnamomum cassia*, which is biochemically from *Cinnamomum verum* [40]. Nevertheless, many studies reported cinnamaldehyde as the hypoglycaemic active ingredient. Cinnamaldehyde may both stimulate insulin secretion and improve insulin sensitivity [41]. Like metformin, cinnamaldehyde reduces gluconeogenesis and improves carbohydrate and liver lipid metabolism. Larger and more homogeneous clinical studies may confirm the use of cinnamon in the treatment of diabetes.

Another promising spice for blood sugar control is turmeric (*Curcuma longa L.*). A systematic review described more than ten clinical trials validating the benefits of turmeric on postprandial hyperglycemia, fasting, glycated haemoglobin and insulin resistance [42]. The spice contains curcumin that significantly reduces fasting glycaemia, glycated haemoglobin and insulin resistance after 3, 6 and 9 months of treatment [42]. In addition, when curcumin is administered with piperine, which improves intestinal absorption, it reduces serum LDL concentrations.

3.4. Tea for reducing the intestinal absorption of glucose

Consumption of tea (*Camellia sinensis (L.) Kuntze*) has been associated with a reduced risk of developing T2D and an improvement of glucose tolerance. Drinking three cups (600 mL) of black tea per day for 12 weeks had a significant reduction in glycated haemoglobin, fasting blood sugar, total cholesterol, as well as improved immune function in patients with T2D [43]. The anti-diabetic action of tea could be ascribed to its high polyphenol content, and in particular to epigallocatechin-3-gallate, an antioxidant which reduces the intestinal absorption of glucose. However, these results still need to be validated by other clinical studies.

4- The hidden treasures of sea

4.1. Insulin-sensitizers and lipid-lowering agents from sponges and algae.

It has been estimated that around 13,000 molecules originate from marine organisms, of which around 3,000 have pharmacological activity [44]. Some compounds are currently used in clinics such as cytarabine, an anti-cancer drug from the Florida sponge (*Cryptotethia crypta*). Another is Omega 3 Acid Ethyl Ester (EEAO), a compound prescribed as a medicine to reduce hypertriglyceridemia. EEAO results from the eicosapentaenoic and docosahexaenoic acids, two polyunsaturated n-3 fatty acids derived from microalgae from the *Prymnesiophyte* family. This reservoir of molecules from the marine organisms would unveil future hypoglycaemic agents and insulin-sensitizers, as illustrated by the promising results from preclinical and clinical studies in **Table 3**.

4.2. Phlorotannins from brown algae as inhibitors of intestinal glucose absorption

Several brown algae including *Ecklonia cava*, *Ascophyllum nodosum* and *Fucus vesiculosus*, contain phlorotannins and polyphenolic compounds, which inhibit alpha amylase and alpha-glucosidase. Clinical studies revealed that ingestion of a phlorotannin (dieckol) extract from *Ecklonia cava* in patients with T2D significantly reduces post-meal hyperglycaemia and may prevent the development of cardiovascular risks by reducing the levels of LDL, and improving HDL concentrations [45].

4.3. Phenolic compounds from brown algae as inhibitors of DPP-4.

DPP-4 inhibitors (gliptins) have been developed to enhance the incretin effect in patients with T2D. These inhibitors represent alternative drugs for patients with risk of hypoglycaemia, after failure of metformin. For this reason, many molecules of this class are currently under development. The search for natural DPP-4 inhibitors offers an opportunity to enrich this class of new drugs, which may be less expensive and better tolerated by patients. Three brown algae, *Padina sulcata*, *Sargassum binderi* and *Turbinaria conoides* could contain these future inhibitors [46]. Each of the three brown algae contains phenolic compounds that effectively inhibit DPP-4. Their identification could therefore allow this class of molecules to extend the list of compounds of natural origin with hypoglycaemic effects.

5. Conclusion

The hypoglycaemic effects of plant extracts, algae and peptides from venoms, as observed in preclinical and clinical studies, indicate future development of new anti-diabetics. Research in animals with highly performant physiology may also be promising for leading to anti-diabetic drugs. Investigation of high-performant metabolism in certain animals such as the hummingbird, for example, could lead to original discoveries of effective drugs. After feeding, the peak blood sugar in the hummingbird can reach 40 mmol / L with HbA1c levels of 4.5% [47]. The HbA1c values are higher than those measured in most birds, but nevertheless lower than those recorded in a normoglycemic man. The hummingbird, a small bird, can also very quickly metabolize 75% of these fat stores when it flies for more than 20 hours. To manage these metabolic needs without developing diabetes, liver disease, and hyperlipidaemia, it is suggested that the hummingbird have high-performance hepatic metabolic machinery [48]. Understanding this machinery could provide a better understanding of glycemic control in diabetes, and also find new therapeutic targets. In view of the diversity of existing animal and plant species, which has not yet been studied, research into the treatment of diabetes has a bright future ahead.

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