Antidiabetic Naphthoquinones and Their Plant Resources in Thailand

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Diabetes mellitus is the seventh leading cause of death globally. Ninety percent of the diabetic population suffers from type-2 diabetes, which still needs an effective, safe and economical oral hypoglycemic therapy. Plants are rich sources of various therapeutic molecules. More than 400 medicinal plants of interesting phytochemical diversity have been reported for their antidiabetic potential. Naphthoquinones are a group of phytochemicals, which have a wide range of pharmacological potential, including antidiabetic activity. Naphthoquinones exert their antidiabetic effects through various mechanisms such as the inhibition of α-glucosidase and protein tyrosine phosphatase 1B, increased glucose uptake in myocytes and adipocytes via glucose transporter type 4 (GLUT4) and GLUT2 translocations, enhanced peroxisome proliferator-activated receptor gamma (PPARγ) ligand activity, and by normalizing carbohydrate metabolizing enzymes in the liver. Moreover, naphthoquinone inhibits adipogenesis by both upstream and downstream regulation to control obesity, which is one of the important risk factors for diabetes. Naturally occurring naphthoquinones, as well as their plant sources, are therefore of interest for exploring their antidiabetic potential. The present review aims to overview the antidiabetic potential of naphthoquinones and their plant resources in Thailand.

Key words hypoglycemic; medicinal plant; naphthoquinone; adipogenesis; obesity

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic hyperglycemic disease, characterized by the altered metabolism of carbohydrates, lipids and proteins due to a defect of insulin secretion or by body tissue resistance to insulin. Two forms of diabetes (type-1 and type-2) differ in their pathogenesis, but hyperglycemia is a common symptom in both. Type-1 DM is due to the loss of insulin-secreting beta cells, whereas type-2 DM is due to an impairment of insulin secretion either with or without the impairment of insulin action. In 2015, more than 4 million cases of DM were reported in Thailand, with a DM prevalence of 8% in people between 20 and 79 years old. The only treatment for type-1 DM is insulin administration, whereas type-2 DM can be treated with commercially available oral antidiabetic drugs. However, many problems are associated with the long-term use of the currently available hypoglycemic drugs, such as their cost and cardiac hazards. It is therefore a challenging task to find a proper therapeutic molecule devoid of the undesirable adverse effects of existing drugs.

Plants are rich sources of various therapeutic molecules. More than 400 medicinal plants have been reported for their antidiabetic potential but the mechanisms of action are known in only 109 of these plants. Particular phytochemicals have been identified in plants having antidiabetic potential, i.e., alkaloids, terpenoids, flavonoids, polysaccharides and naphthoquinones. Thailand is among the world’s richest nations in natural biodiversity resources, due to its unique geographical location. Thai traditional medicines obtained from natural biological resources, especially from medicinal plants, and play an important role in both the public health and the economy of the country. In 2013, the export value of Thai traditional medicines and herbs was $8.06 million USD. Thai flora consist of nearly 10250 described species, which makes up approximately 5% of the diversity in the entire world. Many plants containing naphthoquinone compounds are found in Thailand, and these have been used both as single ingredient preparations or in polyherbal formulations for the treatment of various disorders, including DM. In this paper, the authors put emphasis on summarizing the antidiabetic potential of naphthoquinones and their plant resources, and offer mechanistic insight into the role of naphthoquinones in diabetes amelioration.

2. Naphthoquinones Containing Plants in Thailand

Naphthoquinones are biologically active naturally occurring compounds found in various plant families, including Avicenniaceae, Acanthaceae, Balsaminaceae, Bignoniaceae, Boraginaceae, Droseraceae, Ebenaceae, Juglandaceae, Lythraceae, Nepenthaceae and Plumbaginaceae. The common naphthoquinones found in these plant families are shown in Figs. 1–6. They are biosynthesized via various...
biosynthetic pathways, such as the acetate and malonate pathway for plumbagin and shikimate pathway for lawsone. Known naphthoquinone-containing plants are summarized in Table 1. Some of these exhibited antidiabetic activity in previous studies. They have also been reported to possess other pharmacological effects, such as antimicrobial, antiviral, anti-inflammatory, antipyretic, analgesic, antioxidant, antihemolytic, immunomodulatory, antiallergic, neuroprotective, antiglycation, and antiobesity activities

3. Antidiabetic Potential of Naphthoquinone-Containing Plants in Thailand

Due to their unique phytochemical diversity, plants or natural medicines are considered to be more effective in treating chronic diseases, including DM. *Rhinacanthus nasutus* (L.) KURZ (Family Acanthaceae), a medicinal plant native to Thailand, has been traditionally used in the treatment and cure of several disorders, including DM. R. nasutus has been reported to express various biological activities, as shown in Table 2. Rao et al. extensively studied a methanol extraction of *R. nasutus* leaf (200 mg/kg) for various antidiabetic parameters in the streptozotocin (STZ) induced diabetic rat model. The leaf extract markedly reduced the fasting sugar level, and normalized both the altered lipid profile and the level of antioxidant enzymes, i.e., superoxide dismutase, catalase, and glutathione peroxidase in diabetic rats. The methanol extract (200 mg/kg) was also effective in normalizing the levels of mitochondrial (succinate dehydrogenase, glutamate dehydrogenase and glucose-6-phosphate dehydrogenase) and liver (glucokinase, phosphofructokinase, and pyruvate kinase) enzymes, as well as the glycogen level in diabetic rats. Moreover, the same dose of methanol extract significantly normalized the level of liver function markers and protein contents in the liver tissue of diabetic rats.

The major phytoconstituents in *R. nasutus* are 1,4-naphthoquinone esters, namely rhinacanthins (Fig. 1). Rhinacanthin-C (3), rhinacanthin-D (4) and rhinacanthin-N (12) are the marker naphthoquinones in *R. nasutus* leaves. Rhinacanthin-C is a reddish-yellow, oily 1,4-naphthoquinone found as a major naphthoquinone in the leaves and roots of *R. nasutus*. Recently, rhinacanthin-C (5, 20 mg/kg/d) has been reported
for its hypoglycemic, hypolipidemic, and pancreatic protective effects in STZ nicotinamide induced diabetic rats. Rhinacanthin-C lowered the blood glucose level and lipid profile, and also exerting a pancreatic protective effect by reducing the level of inflammatory and apoptosis mediators, i.e., tumor necrosis factor alpha (TNFα), Ikkβ, and caspase-3 in diabetic rats. An enhanced insulin level was also observed, due to a higher glucose transporter type 2 (GLUT2) level in the pancreas. It has thus been concluded that rhinacanthin-C exerts its anti-diabetic activity by different mechanisms, i.e., increased glucose uptake in adipocytes, and pancreatic protection by enhanced antioxidative enzymes, and cellular apoptotic mediators. Currently, our group is working on the antidiabetic potential of a rhinacanthin-rich extract and its marker compounds, i.e., rhinacanthin-C, rhinacanthin-D and rhinacanthin-N. This rhinacanthins-rich extract exhibited α-glucosidase inhibitory activity (IC_{50} value of 25.0 µg/mL) almost equivalent to that of purified rhinacanthin-C (IC_{50} value of 22.6 µg/mL), but stronger than that of the standard drug, acarbose (IC_{50} value of 395.4 µg/mL). Furthermore, the rhinacanthin-rich extract and rhinacanthin-C, being non-competitive α-glucosidase inhibitors showed synergistic activity with acarbose (a competitive inhibitor). In an antiglycation assay, the rhinacanthin-rich extract (IC_{50} value of 39.7) and
Rhinacanthin-C (IC$_{50}$ value of 37.3 µg/mL) showed a higher inhibitory effect than that of the positive control, rutin (IC$_{50}$ value of 41.5 µg/mL). Furthermore, the rhinacanthin-rich extract and rhinacanthin-C were also studied for their glucose uptake stimulatory effect in 3T3-L1 and L6 cells. The results indicated that the rhinacanthin-rich extract (20 µg/mL) and rhinacanthin-C (20 µg/mL) enhanced glucose uptake in 3T3-L1 adipocytes, which was comparable to standard insulin (0.58 µg/mL). In contrast, rhinacanthin-rich extract (2.5 µg/mL) and rhinacanthin-C (2.5 µg/mL) exhibited stronger activity for enhanced glucose uptake in L6 myotubes than standard insulin (2.9 µg/mL) and metformin (219.5 µg/mL). Moreover, the rhinacanthin-rich extract and rhinacanthin-C were also evaluated for adipogenic inhibition in 3T3-L1 adipocytes. The results indicated that both the rhinacanthin-rich extract and rhinacanthin-C at 5, 10 and 20 µg/mL showed satisfactory dose dependent adipogenic inhibition.

*Kigelia africana* (LAM.) BENTH. (Family Bignoniaceae), a medicinal and ornamental tree native to Thailand and Africa, has been traditionally used in the treatment of several disorders including DM. The phytochemical profile of *K. africana* contains over 145 phytochemicals, which have been purified from its various parts. One of the major chemical constituents of *K. africana* are naphthoquinones, which are shown in Fig. 2. Due to its unique phytochemical diversity, *K. africana* has been reported to possess various biological activities (Table 2). A methanol extract (250, 500 mg/kg) of *K. africana* flower has been reported as showing antidiabetic po-
The results indicated that the extract markedly reduced its antidiabetic potential in an alloxan induced diabetic rat leaf extract (100–400 mg/kg) has been tested for K. africana the glycemic level and lipid profile of the rats. In addition, tal period of 21 d, including Thailand. Various biological activities have been treatment of various diseases in many regions of the world, plant native to China, has traditionally been used for the potential in STZ induced diabetic rats. During an experimen-

Table 2. Biological Activities of Naphthoquinone-Containing Plants in Thailand

<table>
<thead>
<tr>
<th>Plant name</th>
<th>Part(s)</th>
<th>Naphthoquinone(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kigelia africana (Lam.) Benth. (syn. K. pinnata DC.)</td>
<td>Root, wood, fruit</td>
<td>kigeloin (16), isokigeloin (17), kigeloinine (18), 2-(1-hydroxyethyl)naphtho(2,3-b) furan-4,9-dione (19), pinnatal (20), isopinnatal (21), lapachol (22), dehydro-α-lapachone (23) and 2-acetylnaphtho [2, 3-b] furan-4,9-quinone (24), tecomaquinone (25)19–43</td>
</tr>
<tr>
<td>Diospyros kaki L.</td>
<td>Root and wood</td>
<td>plumbagin (26), naphthazarin (27), dichlon (28), 2-bromo-1,4-naphthoquinone (29), 2,3-dihydro-1,4-naphthoquinone (30), methyl juglone (31), isodiospyrin (32), mamegaki-none (33), shinanalone (34)46,47</td>
</tr>
<tr>
<td>Impatiens balsamina L.</td>
<td>Whole plant</td>
<td>plumbagin (26), 6-hydroxyplumbagin (35), 3,3-biplumbagin (36), elliptinone (37), 3,8-dihydroxy-6-methoxy-2-isopropyl-1,4-naphthoquinone (38), 5,7-dihydroxy-8-methoxy-2-methyl-1,4-naphthoquinone (39)48–52</td>
</tr>
<tr>
<td>Lawsonia inermis L.</td>
<td>Root</td>
<td>lawsone (40), methylene-3,3′-bilawsone (41), 2-methoxy-1,4 naphthoquinone (42), impatienol (43)53</td>
</tr>
</tbody>
</table>
| I. balsamina L. | Leaf, seed, plant | antipruritic, anti-anaphylactic, antioxidant, antimicrobial, anticancer activity. These experiments show that

potential in STZ induced diabetic rats. During an experimental period of 21 d, K. africana extract successfully normalized the glycemic level and lipid profile of the rats. In addition, K. africana leaf extract (100–400 mg/kg) has been tested for its anti-diabetic potential in an alloxan induced diabetic rat model. The results indicated that the extract markedly reduced the blood glucose level in the diabetic rats. In a separate study, extracts of K. africana leaves, using acetone, ethanol, chloroform, and water, were tested for α-amylase inhibition, the ethanol extract (500 µg/mL) showed the highest α-amylase inhibition.

Diospyros kaki L. (Ebenaceae), a particular fruit-producing plant native to China, has traditionally been used for the treatment of various diseases in many regions of the world, including Thailand. Various biological activities have been reported for D. kaki, as shown in Table 2. Its phytochemical profile contains a number of naphthoquinones, which have been isolated from different parts of the plant (Fig. 3). Deng et al. investigated the antidiabetic activity of various extracts (ethanol, ethyl acetate, butanol and water) of D. kaki and found that the extracts markedly reduced hyperglycemia and increased the insulin sensitivity index in STZ induced diabetic rats. Jung et al. studied the effect of 5% w/w D. kaki leaf powder in mice for a period of 35 d and found that the leaf powder reduced both blood sugar and lipid profiles of the mice. The hypoglycemic effect was additionally related to a reduced level of gluconeogenesis enzymes and increased level of glycogen. It also decreased lipogenesis by decreasing peroxisome proliferator-activated receptor gamma (PPARγ); inhibiting gene expression and reducing the lipogenic enzyme activity. These experiments show that D. kaki leaf powder can successfully reduce the risk of obesity-associated type 2 DM.

Plumbagnaceae is a diverse family of 24 genera and 775 species, many of which are naphthoquinone-containing plants. Plumbago zeylanica L. and Plumbago indica L. are
two well-known species found in Thailand. Naphthoquinones (Fig. 4) are the principal chemical constituents responsible for the pharmaceutical potential of P. zeylanica and P. indica (Table 1). Plumbago extracts and their purified naphthoquinones have been reported to exhibit various pharmacological activities (Table 2), including against DM. Published reports evaluating antidiabetic effects are available only for P. zeylanica. Olagunju et al. demonstrated the antidiabetic activity of an ethanol extract of P. zeylanica root (400 mg/kg) in STZ induced diabetic rats. This extract controlled glycermia by reducing glycolytic enzyme levels (hexokinase, phosphofructokinase, pyruvate kinase and lactate dehydrogenase) and increasing the synthesis of muscular proteins.138) Zarmouh et al. studied the effect of an ethanol extract of P. zeylanica root (100, 200 mg/kg) on hyperglycemia and liver enzyme levels in STZ induced diabetic rats.139) The results indicated that the ethanol extract normalized the levels of liver enzymes (hexokinase, decreased hepatic glucose-6-phosphatase, serum acid phosphatase, alkaline phosphatase and lactate dehydrogenase) in diabetic rats.139) Furthermore, it was confirmed that the antidiabetic potential of extracts from P. zeylanica roots is due to their principal naphthoquinone i.e., plumbagin (26).140) The study supporting this was performed in STZ induced diabetic rats. Plumbagin (15, 30 mg/kg) exerted antidiabetic effects by enhancing insulin secretion from β-cells. Along with alterations of other biochemical parameters, plumbagin significantly normalized the levels of carbohydrate metabolism enzymes i.e., glucose-6-phosphatase, fructose-1,6-bisphosphatase, and hexokinase. The major antidiabetic mechanisms of plumbagin were explained by restoring the expression and translocations of intestinal α-glucosidase, and stimulating glucose uptake in muscles and adipocytes, probably via GLUT4 translocation.130,132) TNFα, IkκB and caspase-3 reduction in the pancreas of diabetic rats interlink anti-inflammatory activity to antidiabetic potential, while antioxidant and GLUT2 enhancement in the pancreas sensitize insulin secretion to control glycermia.129) Plumbagin exerts an antidiabetic effect via GLUT4 translocation, and normalizing serum and hepatic carbohydrate metabolizing enzymes.143) Shikonin (47) is a naturally occurring 1,4-naphthoquinone, which contributes to the purple color of Lithospermum erythrorhizon SIEBOLD & ZUCC. (Family Boraginaceae) a native plant of China. This compound is a potent antidiabetic molecule that has been investigated by different researchers for a range of antidiabetic mechanisms. Kamei et al. studied the glucose uptake enhancing effects of shikonin in adipocytes and cardiomyocytes. Their results indicated that shikonin (60 μM) significantly stimulated glucose uptake in adipocytes and cardiomyocytes through a tyrosine kinase-dependent pathway by inducing Thr-308 and Ser-473 phosphorylation of Akt.140) Oberg et al. studied the glucose uptake stimulation potential of shikonin in L6 myotubes and also its hypoglycemic activity in diabetic rats. Shikonin (1 μM) enhanced glucose uptake in L6 myotubes via calcium influx and a GLUT4 translocation mechanism. Furthermore, in the same study shikonin (10 mg/kg intraperitoneally for 4 d) markedly normalized blood sugar levels in diabetic rats.140) Another interesting antidiabetic mechanism reported for shikonin is its insulin-like action through the inhibition of the phosphatidylinositol-3,4,5-triphosphate (Pt-3,4,5-P3) phosphatase pathway, which involved the deletion of the tensin homolog on chromosome 10. Shikonin also caused the accumulation of Pt-3,4,5-P3, the activation of protein kinase B, and inhibited several protein phosphatases in different cell systems.130) Hyperglycemia and hyperlipidemia are prime identifying characteristics in the progression of type-2 DM and chronic cardiovascular disorders.132) Insulin resistance, the main cause of type-2 DM is linked with the release of free fatty acids and proinflammatory cytokines from adipose tissues in subjects with obesity or excessive adiposity, which stimulates beta cells to over-secrete insulin and leads to a reduction in receptors.132) Rhinacanthin-C has recently been reported to inhibit adipogenesis in 3T3-L1 adipocytes.132) Shikonin (IC50 value of 1.1 mM) has been documented as having an anti-obesity effect in the diabetic animals.144,145) Another in vivo experiment was performed by Chauhan et al. in alloxan induced diabetic rats to study the effect of a methanol leaf extract (600 mg/kg) of L. inermis.146) The results showed that the methanol extract markedly normalized blood sugar levels and the lipid profile in diabetic rats. Furthermore, an in vitro α-amylase inhibition study indicated that a methanol extract of L. inermis had equivalent inhibitory activity to the standard drug, acarbose.147)

4. Antidiabetic Mechanisms of Naphthoquinones

DM is a multifactor chronic disease that necessitates multidimensional therapeutic strategies. Therefore, a molecule that acts on more than one mechanism is considered to be an ideal candidate when being considered for antidiabetic drug development. Naphthoquinone-containing extracts and purified naphthoquinones exert their antidiabetic activity through several mechanisms of action, as summarized in Fig. 7. Rhinacanthin-C expresses antidiabetic activity by the inhibition of intestinal α-glucosidase, and stimulating glucose uptake in muscles and adipocytes, probably via GLUT4 translocation.130,132) TNFα, IkκB, and caspase-3 reduction in the pancreas of diabetic rats interlink anti-inflammatory activity to antidiabetic potential, while antioxidant and GLUT2 enhancement in the pancreas sensitize insulin secretion to control glycermia.129) Plumbagin exerts an antidiabetic effect via GLUT4 translocation, and normalizing serum and hepatic carbohydrate metabolizing enzymes.143) Shikonin (47) is a naturally occurring 1,4-naphthoquinone, which contributes to the purple color of Lithospermum erythrorhizon SIEBOLD & ZUCC. (Family Boraginaceae) a native plant of China. This compound is a potent antidiabetic molecule that has been investigated by different researchers for a range of antidiabetic mechanisms. Kamei et al. studied the glucose uptake enhancing effects of shikonin in adipocytes and cardiomyocytes. Their results indicated that shikonin (60 μM) significantly stimulated glucose uptake in adipocytes and cardiomyocytes through a tyrosine kinase-dependent pathway by inducing Thr-308 and Ser-473 phosphorylation of Akt.140) Oberg et al. studied the glucose uptake stimulation potential of shikonin in L6 myotubes and also its hypoglycemic activity in diabetic rats. Shikonin (1 μM) enhanced glucose uptake in L6 myotubes via calcium influx and a GLUT4 translocation mechanism. Furthermore, in the same study shikonin (10 mg/kg intraperitoneally for 4 d) markedly normalized blood sugar levels in diabetic rats.140) Another interesting antidiabetic mechanism reported for shikonin is its insulin-like action through the inhibition of the phosphatidylinositol-3,4,5-triphosphate (Pt-3,4,5-P3) phosphatase pathway, which involved the deletion of the tensin homolog on chromosome 10. Shikonin also caused the accumulation of Pt-3,4,5-P3, the activation of protein kinase B, and inhibited several protein phosphatases in different cell systems.130) Hyperglycemia and hyperlipidemia are prime identifying characteristics in the progression of type-2 DM and chronic cardiovascular disorders.132) Insulin resistance, the main cause of type-2 DM is linked with the release of free fatty acids and proinflammatory cytokines from adipose tissues in subjects with obesity or excessive adiposity, which stimulates beta cells to over-secrete insulin and leads to a reduction in receptors.132) Rhinacanthin-C has recently been reported to inhibit adipogenesis in 3T3-L1 adipocytes.132) Shikonin (IC50 value of 1.1 mM) has been documented as having an anti-obesity effect in the diabetic animals.144,145) Another in vivo experiment was performed by Chauhan et al. in alloxan induced diabetic rats to study the effect of a methanol leaf extract (600 mg/kg) of L. inermis.146) The results showed that the methanol extract markedly normalized blood sugar levels and the lipid profile in diabetic rats. Furthermore, an in vitro α-amylase inhibition study indicated that a methanol extract of L. inermis had equivalent inhibitory activity to the standard drug, acarbose.147)
in 3T3-L1 by inhibiting the accumulation of triglycerides via the inhibition of the FABP4 and LPL gene expression, both of which are involved in lipid metabolism. It has also been reported that shikonin inhibits adipogenesis by both up-stream (SREBP1C) and downstream regulation (PPARγ and CCAAT/enhancer binding protein alpha (C/EBPα)).

Various synthetic naphthoquinones have also been reported upon due to their antidiabetic potential. For example, 5,8-di-acetyloxy-2,3-dichloro-1,4-naphthoquinone (48) was obtained through a screening of numerous chemical libraries, consisting of almost 4500 natural and synthetic molecules. This compound (10 µM) was found to be a potent insulin receptor activator and glucose uptake enhancer in adipocytes. It has a strong affinity to bind with a receptor kinase and trigger its activity by Akt and extracellular signal-regulated kinase (ERK) phosphorylations. The hypoglycemic mechanisms were further validated through an in vivo experiment in the same study.

Protein tyrosine phosphatase 1B (PTP1B) is an important enzyme in insulin signaling and resistance, which relates to type-2 diabetes. 1,2-Naphthoquinone (IC₅₀ of 1.64 µM) was identified in the course of a high throughput screening, and a group of 1,2-naphthoquinone (49) derivatives were synthesized from 1,2-naphthoquinone, and found to be potential inhibitors of PTPB1 at very low concentrations. Later derivatization of the molecule showed that molecules having phenyl or indole functional groups were more potent as compared to those having nitrogen or oxygen functional groups.

Peroxisome proliferator-activated receptor gamma (PPARγ) ligand activity also provides an interesting target for the treatment of metabolic disorders such as diabetes, obesity, inflammatory diseases and cancer. Recently, a series of compounds with 2-hydroxy-1,4-naphthoquinone (50) as an acidic group were predicted to express PPARγ ligand activity; a hypothesis which was later validated experimentally. Furthermore, it was concluded that the hydrogen bonding of the compound with the receptor is important for its activation.

5. Future Prospects

The current literature review has summarized that extracts from most naphthoquinone-containing plant have antidiabetic effects. However, some of them remain to be fully explored. In this context, there are some reports on the antidiabetic activity from two plant species in the family Nepenthaceae, i.e., Nepenthes bicalcarata and N. khasiana, which are not available in Thailand. Thai native species of Nepenthes, including, N. ampullaria, N. gracilis, N. mirabilis, N. smilessi, and N. thorelii, currently lack investigation into their potential antidiabetic activity. There is therefore a need to determine the possible naphthoquinone-based antidiabetic and antiobesity activity of these species. Previously isolated naphthoquinones, such as the major naphthoquinones from I. balsamina and L. inermis, are suggested as candidates to be evaluated for their mechanism of antidiabetic action. In conclusion, naphthoquinones are ideal candidates for antidiabetic drug development due to their diverse therapeutic potential and multimechanism antidiabetic activity.

Conflict of Interest
The authors declare no conflict of interest.

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