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Revisiting New Classes of Chalcones from Antidiabetic Perspectives

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ABSTRACT

Elevated blood sugar levels and a plethora of other, more diverse diseases, including changes to protein, carbohydrate, and lipid metabolism, are the only hallmarks of diabetes mellitus. Recent research has shown that mice lacking PTP1B had better glucose tolerance, less diet-induced obesity, and insulin sensitivity in general. In the therapy of serious diabetic problems, natural chalcones have recently been discovered, which have superior selectivity and do not affect pharmacokinetics. This is in response to the present demand for improved PTP-1B inhibitors. No appropriate formulation has been developed for the inhibitors based on natural products chalcones as they have not been tested clinically for toxicological characteristics. The review article has extensively covered various unknown natural chalcone compounds, such as kuwanon J, kuwanon R, kuwanon V, isoliquiritigenin, xanthoangelol, xanthoangelol D, xanthoangelol E, xanthoangelol F, xanthoangelol K, 4-hydroxyderricin, 5,4'-dihydroxy-6,7-furanbavachalcone, licochalcone A, licochalcone B, licochalcone C, licochalcone D, licochalcone E, echinatin, laxichalcone, brousochalcone, macdentichalcone, (2E)-1, 1-(5,7-dihydroxy-2,2-dimethyl-2H-benzopyran-8-yl)-3-phenyl-2-propen-1-one, often known as 2E(abyssinone-VI-4-O-methyl ether, 1-(5,7-dihydroxy-2,2,6-trimethyl-2H-benzopyran-8-yl)-3-(4-methoxyphenyl)-2-propen-1-one) show great promise as a diabetic medication because it can inhibit insulin degradation by targeting the therapeutic target protein tyrosine phosphatase 1B (PTP-1B). These chalcone-based PTP-1B inhibitors derived from natural products are not currently used in clinical trials and have not attracted much interest from contemporary medicine due to a lack of clinical investigation into their toxicological profiles necessary to create an appropriate formulation. These chalcone-based PTP-1B inhibitors may soon unlock new opportunities in diabetotherapeutics.

Keywords: Chalcone, Molecular targets, Inhibitors, Antidiabetic, Mechanisms, PTP1B

INTRODUCTION

Diabetes Mellitus (DM) is exclusively characterized by enhanced plasma sugar levels along with several groups of heterogeneous disorders such as alteration in the metabolism of proteins, carbohydrates, and lipids.¹ This constant hyperglycemic circumstance leads to enhanced risks of vascular complications and directly affects the blood vessels, eyes, kidneys, heart, and nerves.² A patient suffering from DM experience hepatic gluconeogenesis, reduced uptake of blood glucose by tissues, and impaired insulin secretion which concurrently results in precipitation of symptoms like excessive hunger, random plasma blood sugar level of >200 mg/dL, glucose in the urine, weight loss, and excessive thirst.^{3,4}

In two discrete phases (fasting blood glucose concentration and postprandial blood glucose concentration), the secretion

(magnitude) of insulin takes place from the β -cells of the pancreas.⁵ First, a speedy release of insulin takes place just after the meal (due to rapid augmentation of glucose levels) which is pursued by a sustained phase of circulating concentrations of insulin. In DM, intrinsic problems such as ineffective hyperglycemic and hypoglycemic phases due to fluctuation of two phases of insulin are perceived.⁶ In type-I DM, insulin deficiency leads to failure in the conversion of sugar into its storage form and utilization, whereas failure of proper utilization of secreted insulin is the chief characteristic of type-II DM. In type-II DM, reduced adipose cells and muscle sensitivity toward insulin are the most prominent features.⁷

In the pharmacotherapeutic point of view, insulin sensitizers are the best compounds for the successful treatment of the hyperglycemic conditions that will amplify the muscle and adipose tissue's sensitivity to insulin.⁸ In the modern

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era, glitazones and sulfonylureas are not much effective in the management of hyperglycemic episodes and therefore the need for effective inhibitors is a major challenge.⁹ For diabetotherapy, Protein Tyrosine Phosphatase-1B (PTP-1B) inhibitors, Alpha-glucosidase (AG) inhibitors, Aldose Reductase (AR) inhibitors, and insulin sensitizers are the upcoming preferred options as these compounds prevent the degradation of insulin and prolong the action.¹⁰

ANTI-DIABETIC ACTIVITY

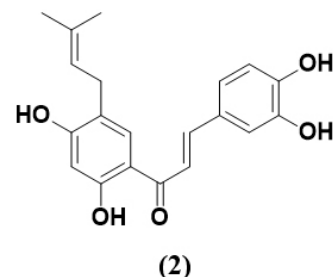
Protein Tyrosine Phosphatase-1B inhibitors

Present-day studies have indicated that PTP1B-knockout animals demonstrated improved glucose tolerance, reduction in diet-induced obesity, and enhanced sensitivity of cells towards insulin.¹¹ Similarly, the administration of PTP-1B anti-sense oligonucleotides showed improved insulin sensitivity and normalized the plasma glucose levels as a result of reduced enzyme expression.¹² Clinical researches have indicated the role of PTP-1B inhibitors (*ertiprotafib*; discontinued from clinical trials due to lack of efficacy and *trodusquemine*; presently under clinical trials) in the dephosphorylation of IR and downregulation of insulin signaling pathway.¹³ The tyrosine mimetic comprising of negatively charged functionalized components like malonates, cinnamates, phosphonates, and carboxylates have been recognized as PTP-1B inhibitors with distinct advantages.¹⁴ These above collective evidence from genetic, pharmaceutical, physiological, and biochemical backgrounds have addressed towards the perspectives of PTP-1B inhibitors as the latest candidates in the management of hyperglycemic episodes and related obesity. This exciting anti-diabetic target (specifically type-II DM) will be of immense significance towards the development of potent low-molecular-weight inhibitors.¹⁵

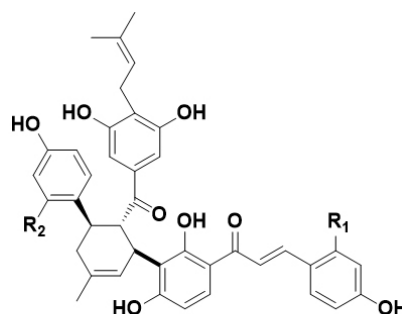
However, several PTP-1B inhibitors are available and reported widely, but poor pharmacokinetic properties and low selectivity remained a challenging issue.¹⁶ For meeting the need for better PTP-1B inhibitors in the current scenario, natural chalcones have been recently identified in the management of major diabetic complications with better selectivity and also without any pharmacokinetic compromise. In modern days, these natural product chalcone-based inhibitors are not under clinical use and they have not received any such attention as they are not explored clinically in terms of toxicological profiles to develop a suitable formulation.

A handful of natural chalcone molecules have been reported to express potent PTP-1B inhibition activity. From the leaf extract of *Broussonetiapapyrifera*, broussochalcone(2) was isolated and screened for PTP-1B inhibitory potential with

an IC_{50} value of 21.5 μ M. The two –OH groups situated at both the rings of the compound are responsible for the inhibitory activity by interacting with the active sites of the enzyme. It was predicted that the inhibitory activity increases with an increase in the number of –OH groups in the pharmacophore.¹⁶



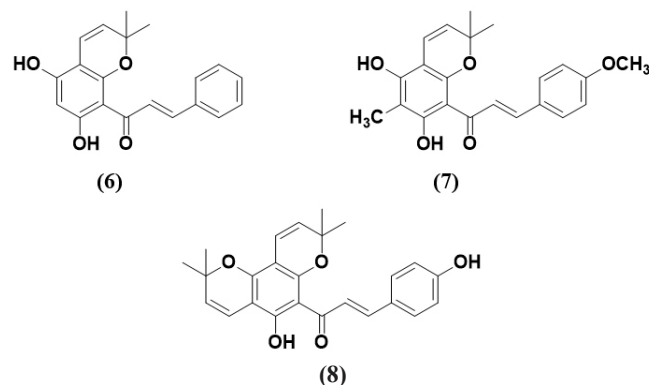
KuwanonJ (3), kuwanon R (4), and kuwanon V (5), the methyl cyclohexene substituted derived Diels-Alder type chalcones, isolated from *Morus bombycis* have demonstrated tremendous PTP-1B inhibitory activity (IC_{50} values in the range of 2.7–13.8 μ M) in a mixed-type mechanism. The presence of the –OH group provides excellent penetration of the molecule into the active site of the therapeutic target and provides an effectual hydrogen bonding interaction with the active-site loop of PTP-1B. It is stated that with an increase in the number of –OH groups in Diels-Alder-type compounds, the pharmacological potential augments simultaneously. The molecule (4) comprising of 7–OH groups produced a dose-independent inhibition in comparison to compound (5) which has 6–OH groups. The compound (3) has one more –OH group at second carbon atom which enhances the potency by 3-folds as compared to compound (5). Compound (3) has better pharmacological efficacy and potency than compound (4) and compound (5).¹⁷



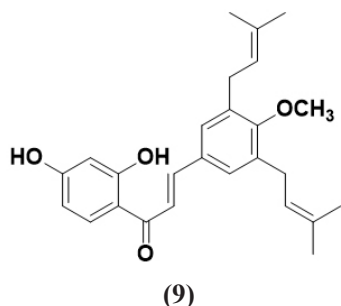
(3) $R_1 = OH$, $R_2 = OH$; (4) $R_1 = H$, $R_2 = OH$; (5) $R_1 = H$, $R_2 = H$

The coumarin based chalcones; (2*E*)-1-(5,7-dihydroxy-2,2-dimethyl-2*H*-benzopyran-8-yl)-3-phenyl-2-propen-1-one (6), (2*E*)-1-(5,7-dihydroxy-2,2,6-trimethyl-2*H*-benzopyran-8-yl)-3-(4-methoxyphenyl)-2-propen-1-one (7), and laxichalcone(8) have presented noteworthy *in vitro*

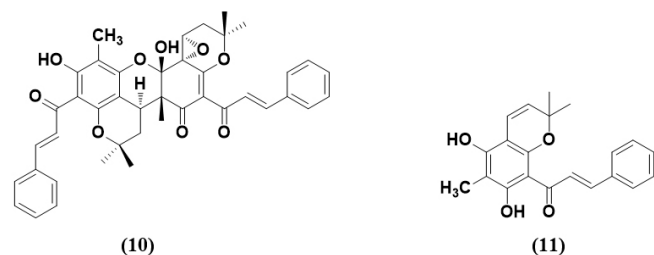
PTP-1B inhibitory activity with IC_{50} values in micromolar concentrations.¹⁸



From the root bark of *Erythrinamildbraedii*, a novel chalcone molecule abyssinone-VI-4-O-methyl ether (9) was isolated and evaluated for *in vitro* PTP-1B inhibitory activity where a remarkable inhibition was seen with an IC_{50} value of 14.8 μ M.¹⁹

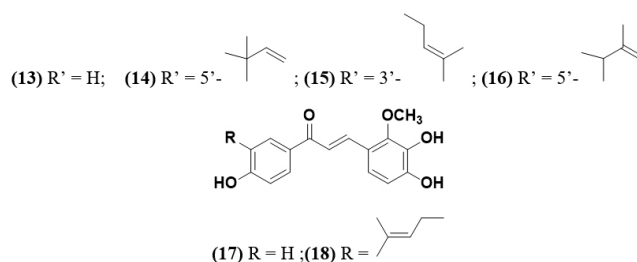
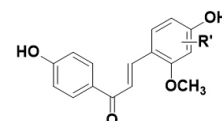
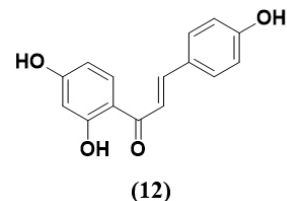


A polycyclic dimeric chalcone comprising of quinonoid moiety isolated from *Macaranga denticulata*, macdentichalcone (10) along with its monomeric biosynthetic precursor 1-(5,7-dihydroxy-2,2,6-trimethyl-2H-1-benzopyran-8-yl)-3-phenyl-2-propen-1-one (11). On *in vitro* PTP-1B inhibitory screening, both the compounds exhibited impressive pharmacotherapeutic activity with IC_{50} values of 21 μ M and 22 μ M, respectively.²⁰



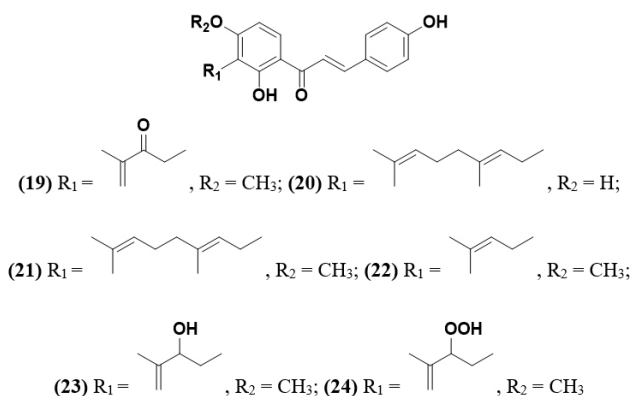
From the leaves of *Glycyrrhiza inflata*, isoliquiritigenin (12), echinatin (13), licochalcone A (14), licochalcone C (15), licochalcone E (16), licochalcone B (17), and licochalcone D

(18), were isolated and reported to be promising candidates for the inhibition of PTP-1B in micromolar concentration.²¹

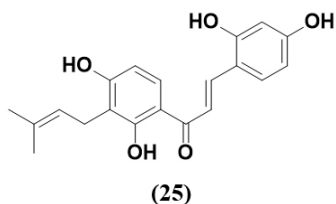


Isoliquiritigenin (12) was investigated to inhibit the anti-diabetic target PTP-1B by preventing the phosphorylation of IR/PI3K/AKT and also inhibiting the oxidation of PTP-1B under insulin-induced adipogenesis stages and insulin-induced adipocyte differentiation of 3T3-L1 cells.²²

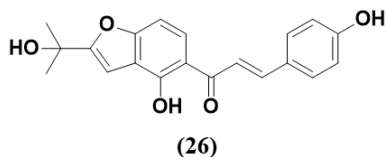
The well-known natural chalcones; xanthoangelol K (19), xanthoangelol (20), xanthoangelol F (21), 4-hydroxyderricin (22), xanthoangelol D (23), and xanthoangelol E (24) displayed amazing *in vitro* PTP-1B inhibition with IC_{50} range 0.82-3.98 μ g/mL in a competitive manner. Docking studies have revealed that the ring-B of the natural chalcones anchors in the pocket of the anti-diabetic target through hydrogen bonds (Arg47 and Asp48) and p-p interactions (Phe182).²³



Chalcone, (*E*)-1-(2,4-dihydroxy-3-(3-methylbut-2-en-1-yl)phenyl)-3-(2,4-dihydroxyphenyl)prop-2-en-1-one(**25**) was isolated from the root bark of *Morus alba* L. along with 21 phenolic compounds. The chalcone exhibited a notable PTP-1B inhibition with an IC_{50} value of 31.61 μ M in a non-competitive manner.²⁴



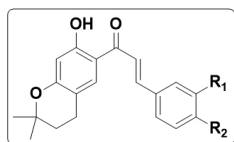
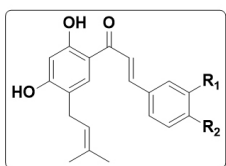
A novel chalcone 5,4'-dihydroxy-6,7-furanbavachalcone (**26**) was isolated along with other polyphenols (isobavachalcone, bavachin, psoralenol, corylifol E, and corylifol A) from the seeds of *Psoralea corylifolia* (known as Bu-Gu-Zhi in traditional Chinese medicine). The novel chalcone expressed *in vitro* PTP-1B inhibition with an IC_{50} value of 14.3 μ M.²⁵



α -glucosidase inhibitors

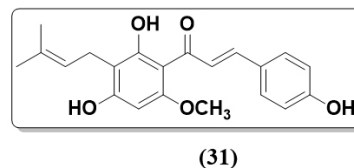
α -glucosidase are carbohydrase located in the brush border epithelium of small intestine that catalyzes the liberation of glucopyranose molecules from carbohydrate substrates by smiting the non-reducing 1,4 linked α -glucose.²⁶ Inhibition of this molecular target will lead to the decreased formation of the glucose content from the dietary carbohydrates that will lead to the suppression of postprandial hyperglycemia. Therefore these “starch blockers” will block the absorption of glucose from the intestines, reduction in the body weight, and control triglyceride levels in diabetic patients.²⁷

From the roots of *Broussonetiapyrifera*, Ryu et al. isolated the chalcones(**27-30**) and their potential to inhibit α -glucosidase was *in vitro* screened. The study showed non-competitive inhibition of the target enzyme with IC_{50} values in the range 5.3-19.1 μ M.²⁸

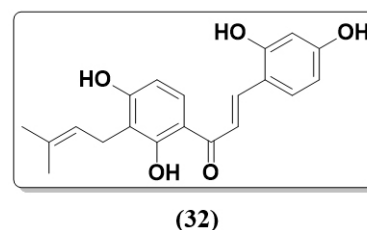


(**27**) R₁ = R₂ = OH; (**28**) R₁ = H, R₂ = OH (**29**) R₁ = R₂ = OH; (**30**) R₁ = H, R₂ = OH

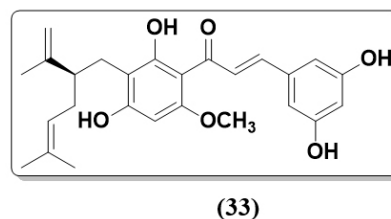
In a screening done by Liu et al., the isolated xanthohumol(**31**) from the beer hops demonstrated noncompetitive and reversible inhibition of α -glucosidase with an IC_{50} value of 8.8 μ M. The prenylatedchalcone also inhibited the liberation of glucose molecules from the maltose in the monolayer caco-2 cell.²⁹



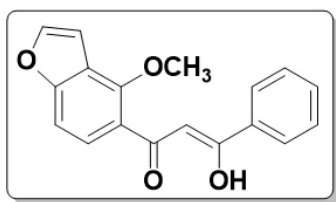
Morachalcone(**32**), a novel chalcone molecule was isolated from *Morus alba* L., showed remarkable α -glucosidase inhibitory activity with an IC_{50} value of 11.85 μ M in a competitive manner. Ha et al. also screened the potential of morachalcone in inhibiting PTP-1B where it exhibited an IC_{50} value of 31.61 μ M in a non-competitive manner.³⁰



Kim et al. screened the ability of the lavandulylatedchalconekurardin(**33**) in inhibiting the glucose liberating enzyme α -glucosidase. The study display inhibition of the target with an IC_{50} value of 57 μ M in a non-competitive manner (K_i = 8.6 μ M). The lavandulyl group at 8-position plays a considerable role on inhibition of the target.³¹

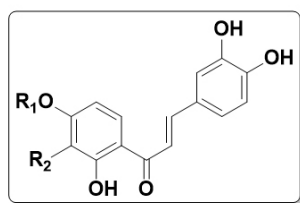


In a bioassay-guided fractionation, pongamol(**34**), a benzofuran containing chalcone isolated from the *Derris indica* root extract have been *in vitro* reported to inhibit the α -glucosidase with an IC_{50} value of 103.5 μ M.³²

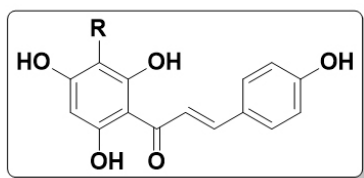


(34)

From the aerial part extract of *Andromachiaignaria*, okanin(35), butein(36), and okanin 4'-O-β-D-glucopyranoside (37) were isolated and screened for α-glucosidase inhibition. The study revealed tremendous inhibition of the enzyme with IC₅₀ values of 0.02 μM, 0.02 μM, and 0.25 μM, respectively.³³

(35) R₁ = H, R₂ = OH; (36) R₁ = R₂ = H; (37) R₁ = -Glu, R₂ = OH

Sun et al. isolated desmethylxanthohumol (38), 3-geranylchalconaringenin (39), and chalconaringenin(40) from *Humulus lupulus* and explored the *in vitro* α-glucosidase inhibitory potential. The compounds successfully inhibited the anti-diabetic target as indicated by the IC₅₀ values of 22.42 μM, 1.08 μM, and 20.02 μM, respectively. The compound (40) expressed docking score of 58 kcal/mol and practically exhibited 50-folds higher activity than that of the standard drug acarbose.³⁴



(38) R = Prenyl; (39) R = Geranyl; (40) R = H

CONCLUSION

A review article describes several highly unknown natural species with great potential for exhibiting antidiabetic activity by selectively modulating the protein tyrosine phosphatase 1B (PTP-1B), a promising therapeutic target that prevents the degradation of insulin. We focus broadly on chalcone compounds. Various electron-withdrawing/donating groups such as -OH, -CH₃, -OCH₃ in the pharmacophore are associated with amino acid residues located in the pharmacophore, the phosphotyrosine loop, structure activity

of chalcone-based PTP-1B inhibitors. No specific predictions on SAR were made in this article. Today, these natural product chalcone-based PTP-1B inhibitors have not been used clinically and have not been clinically evaluated for their toxicological profiles to develop suitable formulations, so much so in modern medicine. These chalcone-based PTP-1B inhibitors are expected to open new avenues for diabetes treatment in the near future.

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Conflict of interest

None declared.

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Authors' Contribution:

Suman Uraiha: Writing, Illustrations

Jyoti Maitry: Editing, Literature Review

Lata Patel Choudhary: Concept, Checking

Yogesh Pounikar: Revisions

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