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Newer Approach For Protein Tyrosine Phosphatase-1B Targeting By Chalcones

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ABSTRACT

Diabetes Mellitus 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. 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. For meeting the need for better PTP-1B inhibitors in the current scenario, natural chalcones have been recently been identified in the management of major diabetic complications with better selectivity and also without any pharmacokinetic compromise. The natural product chalcone-based inhibitors are not under clinical use and they are not explored clinically in terms of toxicological profiles to develop a suitable formulation. The review article has comprehensively focused on some very unknown natural chalcone compounds (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, broussochalcone, macdentichalcone, (2*E*)-1-(5,7-dihydroxy-2,2-dimethyl-2*H*-benzopyran-8-yl)-3-phenyl-2-propen-1-one, (2*E*)-1-(5,7-dihydroxy-2,2,6-trimethyl-2*H*-benzopyran-8-yl)-3-(4-methoxyphenyl)-2-propen-1-one, and abyssinone-VI-4-O-methyl ether) having tremendous potential to exhibit anti-diabetic activity by selectively modulating the promising therapeutic target protein tyrosine phosphatase 1B (PTP-1B) that will prevent the degradation of insulin. In modern days, these natural product chalcone-based PTP-1B inhibitors are not under clinical use and they have not received any such attention in modern-day medicine as they are not explored clinically in terms of toxicological profiles to develop a suitable formulation. In the near future, it is expected that these chalcone based PTP-1B inhibitors will open new avenues of diabetotherapeutics.

Keywords: Chalcone, Diabetes mellitus, Anti-hyperglycemic, Hypoglycemic, Protein Tyrosine Phosphatase, Inhibitors

1. 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 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 and Dipeptidyl Peptidase-4 (DPP-4) inhibitors are the upcoming preferred options as these compounds prevent the degradation of insulin and prolong the action [10].

2. ROLE OF PROTEIN TYROSINE PHOSPHATASE-1B IN DIABETES MELLITUS

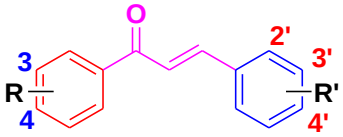
Present-day studies have indicated that PTP1B-knockout animals demonstrated improved glucose tolerance, reduction in diet-induced obesity, and enhanced sensitivity of cells towards insulin [11]. Similarly, the administration of PTP-1B anti-sense oligonucleotides showed improved insulin sensitivity and 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 been 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.

3. NATURAL PRODUCT CHALCONES

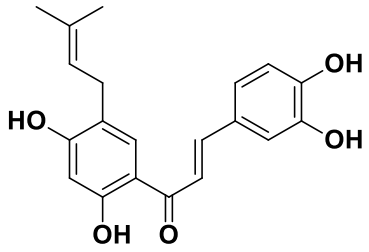
Chalcone **(1)** is a precursor of flavonoid and isoflavonoid originated from Mother Nature [17]. It is also known as 1,3-diphenyl-2-propene-1-one that comprises of an open-chain intermediate in the aurone synthesis [18]. The benzylideneacetophenone component comprising of two aromatic components linked by α, β-unsaturated carbonyl bridge function is the characteristic identity of this scaffold [19]. It is one of the most privileged scaffolds due to feasibility of productive computational studies [20], synthesized at academic laboratory scale (first fabricated as chromophoric products by Kostanecki and Tambor in 19th Century from benzaldehyde and acetophenone) [21], therapeutic targets modulating ability (actions against protozoal infections, bacterial infections, sleep disorder, trypanosomiasis, anxiety, gout, malaria, epilepsy, hypertension, reduced immune response, spasm, diabetes, tuberculosis, leishmaniasis, ulcer, fungal infections, cancer, thrombosis, reactive oxygen species, inflammation, HIV, metastasis, etc.) [22-24], simplicity in the overall product chemistry, structural elucidation of natural products [25], development at industrial or commercial scales [26], hybridization with multiple other scaffolds [27], various non-pharmacological applications [28-29], and ten replaceable hydrogen atoms for producing multiple active compounds [30].



(1)

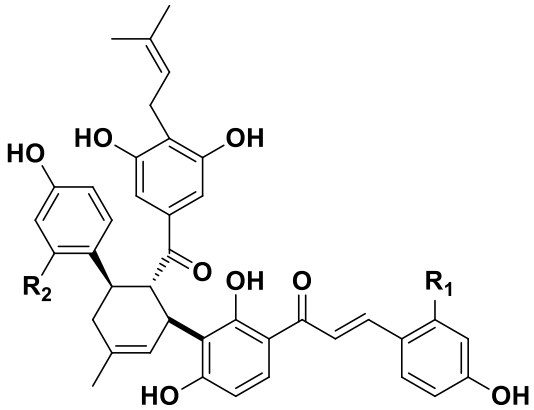
4. CHALCONES AS PTP-1B INHIBITORS

A handful of natural chalcone molecules have been reported to express potent PTP-1B inhibition activity. From the leaf extract of *Broussonetia papyrifa*, broussochalcone **(2)** was isolated and screened for PTP-1B inhibitory potential with an IC_{50} value of 21.5 μM. 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 [31].



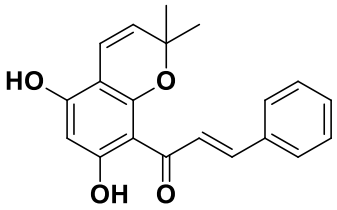
(2)

Kuwanon J **(3)**, kuwanon R **(4)**, and kuwanon V **(5)**, the methylcyclohexene 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 μM) 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)** [32].



(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 [33].



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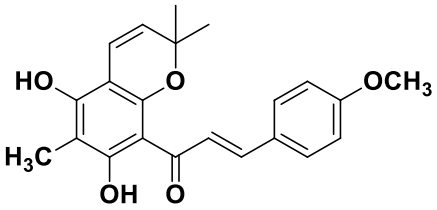

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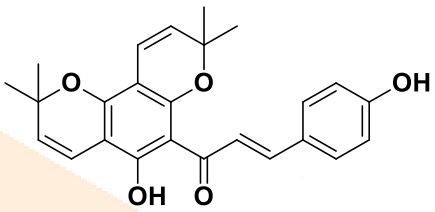
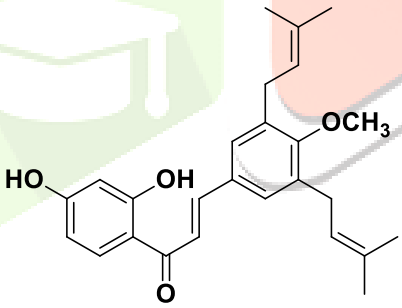


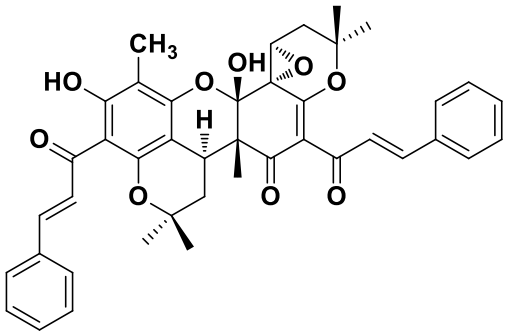
(8)

From the root bark of *Erythrina mildbraedii*, 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 μM [34].



(9)

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-2*H*-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 μM and 22 μM, respectively [35].



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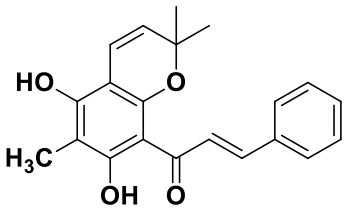
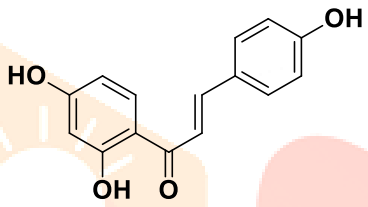
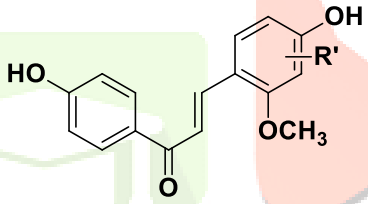


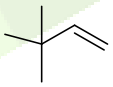
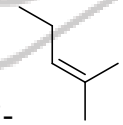
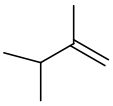
(11)

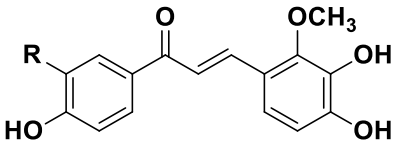
From the leaves of *Glycyrrhiza inflate*, isoliquiritigenin **(12)**, echinatin **(13)**, licochalcone A **(14)**, licochalcone C **(15)**, licochalcone E **(16)**, licochalcone B **(17)**, and licochalcone D **(18)**, were isolated and reported to be promising candidates for the inhibition of PTP-1B in micromolar concentration [36].

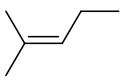


(12)



(13) R' = H ; **(14)** R' = 5'-  ; **(15)** R' = 3'-  ; **(16)** R' = 5'- 

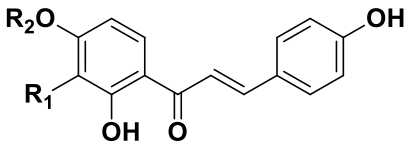


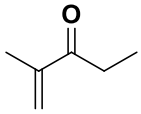
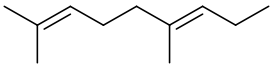
(17) R = H ; **(18)** R = 

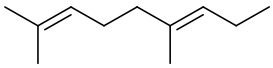
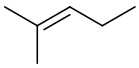
Isoliquiritigenin **(12)** was investigated to inhibit the anti-diabetic target PTP-1B by preventing the phosphorylation of IR/PI3K/AKT and also inhibiting the oxidation of PTP-1B under insulin-induced adipogenesis stages and insulin-induced adipocyte differentiation of 3T3-L1 cells [37].

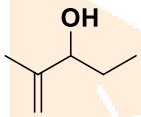
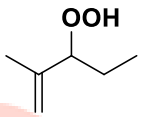
The well known natural chalcones; xanthoangelol K **(19)**, xanthoangelol **(20)**, xanthoangelol F **(21)**, 4-hydroxyderricin **(22)**, xanthoangelol D **(23)**, and xanthoangelol E **(24)** displayed amazing *in vitro* PTP-

1B inhibition with IC_{50} range 0.82-3.98 µg/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 (Arg 47 and Asp 48) and p-p interactions (Phe 182) [38].

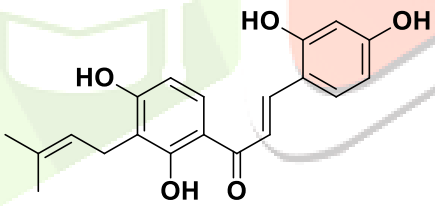


(19) R_1 =  , $R_2 = CH_3$; **(20)** R_1 =  , $R_2 = H$;

(21) R_1 =  , $R_2 = CH_3$; **(22)** R_1 =  , $R_2 = CH_3$;

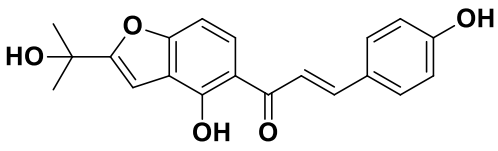
(23) R_1 =  , $R_2 = CH_3$; **(24)** R_1 =  , $R_2 = CH_3$

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 µM in a non-competitive manner [39].



(25)

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 µM [40].



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5. 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, $-CH_3$, $-OCH_3$ 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.

6. REFERENCES

1. Shivhare RS, Mahapatra DK. Medicinal Chemistry-II. Nagpur: ABD Publications Private Limited, 2019. Available at: https://www.flipkart.com/medicinal-chemistry-ii/p/itm7fb62fec19f4a

2. Godbole MD, Mahapatra DK, Khode PD. Fabrication and Characterization of Edible Jelly Formulation of Stevioside: A Nutraceutical or OTC Aid for the Diabetic Patients. Inventi Rapid: Nutraceuticals 2017; 2017(2): 1-9.

3. Kuhite NG, Padole CD, Amdare MD, Jogdand KR, Kathane LL, Mahapatra DK. Hippuric acid as the template material for the synthesis of a novel anti-diabetic 1,3,4-thiadiazole derivative. Indian Journal of Pharmaceutical and Biological Research 2017; 5(3): 42-45. Available at: https://web.p.ebscohost.com/abstract?direct=true&profile=ehost&scope=site&authtype=crawler&jrnl=09767126&AN=136249571&h=iocmZdbvmkKlXnEuL8%2febH8%2bTqCE0laWDmfWvV%2f7qRZrO9YLkQx2rjgKfs4X7KY8XTx6cdgZB3TJIWnkTDUX%2fg%3d%3d&crl=c&resultNs=AdminWebAuth&resultLocal=ErrCrlNotAuth&crlhashurl=login.aspx%3fdirect%3dtrue%26profile%3dehost%26scope%3dsite%26authtype%3dcrawler%26jrnl%3d09767126%26AN%3d136249571

4. Gangane PS, Kadam MM, Mahapatra DK, Mahajan NM, Mahajan UN. Design and formulating gliclazide solid dispersion immediate release layer and metformin sustained release layer in bilayer tablet for the effective postprandial management of diabetes mellitus. International Journal of Pharmaceutical Sciences and Research 2018; 9(9): 3743-3756.

5. Puranik MP, Mahapatra DK. Medicinal Chemistry-III. Nagpur: ABD Publications Private Limited, 2019. Available at: https://www.amazon.in/-/hi/Dr-Mrs-Manisha-P-Puranik-ebook/dp/B08W57NBMS

6. Mahapatra DK, Chhajed SS, Shivhare RS. Development of Murrayanine-Chalcone hybrids: An effort to combine two privilege scaffolds for enhancing hypoglycemic activity. International Journal of Pharmaceutical Chemistry and Analysis 2017; 4(2): 30-34.

7. Mahapatra DK, Dadure KM, Haldar AGM. Uracil substitution on a hippuric acid containing 1,3,4-thiadiazole scaffold: The exploration of the anti-hyperglycemic potential. International Journal of Medical Science in Clinical Research and Review 2018; 1(2): 1-4.

8. Mahapatra DK, Bharti SK. Handbook of Research on Medicinal Chemistry: Innovations and Methodologies. New Jersey: Apple Academic Press, 2017.

9. Mahapatra DK, Bharti SK. Medicinal Chemistry with Pharmaceutical Product Development. New Jersey: Apple Academic Press, 2019.

10. Torrens F, Mahapatra DK, Haghi AK, Editors. Biochemistry, Biophysics, and Molecular Chemistry: Applied Research and Interactions. New Jersey: Apple Academic Press, 2020. Available at: https://www.routledge.com/Biochemistry-Biophysics-and-Molecular-Chemistry-Applied-Research-and/Torrens-Mahapatra-Haghi/p/book/9781774635100

11. Koren S, Fantus IG. Inhibition of the protein tyrosine phosphatase PTP1B: potential therapy for obesity, insulin resistance and type-2 diabetes mellitus. Best Practice & Research Clinical Endocrinology & Metabolism. 2007;21(4):621-40.

12. Taylor SD. Inhibitors of protein tyrosine phosphatase 1B (PTP1B). Current topics in medicinal chemistry. 2003;3(7):759-82. Available at: https://www.ingentaconnect.com/content/ben/ctmc/2003/00000003/00000007/art00004

13. Goldstein BJ. Protein-tyrosine phosphatase 1B (PTP1B): a novel therapeutic target for type 2 diabetes mellitus, obesity and related states of insulin resistance. Current Drug Targets-Immune, Endocrine & Metabolic Disorders. 2001;1(3):265-75.

14. Wang LJ, Jiang B, Wu N, Wang SY, Shi DY. Small molecules as potent protein tyrosine phosphatase 1B (PTP1B) inhibitors documented in patents from 2009 to 2013. Mini reviews in medicinal chemistry. 2015;15(2):104-22.

15. Huijsduijnen RH, Wälchli S, Ibberson M, Harrenga A. Protein tyrosine phosphatases as drug targets: PTP1B and beyond. Expert opinion on therapeutic targets. 2002;6(6):637-47.

16. Sun J, Qu C, Wang Y, Huang H, Zhang M, Li H, Zhang Y, Wang Y, Zou W. PTP1B, a potential target of type 2 diabetes mellitus. Mol. Biol. 2016;5(4):174.

17. Mahapatra DK, Asati V, Bharti SK. Recent therapeutic progress of chalcone scaffold bearing compounds as prospective anti-gout candidates. J Crit Rev. 2019; 6(1): 1-5.

18. Mahapatra, D. K., Bharti, S. K., & Asati, V. (2015). Anti-cancer chalcones: Structural and molecular target perspectives. *European Journal of Medicinal Chemistry*, *98*, 69-114.

19. Mahapatra, D. K., Bharti, S. K., & Asati, V. (2015). Chalcone scaffolds as anti-infective agents: Structural and molecular target perspectives. *European Journal of Medicinal Chemistry*, *101*, 496-524.

20. Mahapatra, D. K., Asati, V., & Bharti, S. K. (2015). Chalcones and their therapeutic targets for the management of diabetes: structural and pharmacological perspectives. *European Journal of Medicinal Chemistry*, *92*, 839-865.

21. Mahapatra, D. K., & Bharti, S. K. (2016). Therapeutic potential of chalcones as cardiovascular agents. *Life Sciences*, *148*, 154-172.

22. Mahapatra, D. K., Bharti, S. K., & Asati, V. (2017). Chalcone derivatives: Anti-inflammatory potential and molecular targets perspectives. *Current topics in Medicinal Chemistry*, *17*(28), 3146-3169.

23. Mahapatra, D. K., Bharti, S. K., Asati, V., & Singh, S. K. (2019). Perspectives of medicinally privileged chalcone based metal coordination compounds for biomedical applications. *European Journal of Medicinal Chemistry*, *174*, 142-158.

24. Mahapatra, D. K., Asati, V., & Bharti, S. K. (2019). An updated patent review of therapeutic applications of chalcone derivatives (2014-present). *Expert opinion on therapeutic patents*, *29*(5): 385-406.

25. Mahapatra DK, Asati V, Bharti SK. Natural and Synthetic Prop-2-ene-1-one Scaffold Bearing Compounds as Molecular Enzymatic Targets Inhibitors against Various Filarial Species. In: Torrens F, Mahapatra DK, Haghi AK, editors. Biochemistry, Biophysics, and Molecular Chemistry: Applied Research and Interactions. New Jersey: Apple Academic Press, 2019.

26. Mahapatra DK, Asati V, Bharti SK. Promising anti-cancer potentials of natural chalcones as inhibitors of angiogenesis. In: Volova TG, Mahapatra DK, Khanna S, Haghi AK, editors. Natural Products Chemistry: Biomedical and Pharmaceutical Phytochemistry. New Jersey: Apple Academic Press, 2020.

27. Mahapatra DK, Asati V, Bharti SK. Chalcone Scaffold bearing Natural Anti-gout Agents. In: Mahapatra DK, Haghi AK, editors. Natural Pharmaceuticals and Green Microbial Technology: Health Promotion and Disease Prevention. New Jersey: Apple Academic Press, 2020.

28. Mahapatra DK, Bharti SK, Asati V. Recent perspectives of chalcone based molecules as protein tyrosine phosphatase 1B (PTP-1B) inhibitors. In: Mahapatra DK, Bharti SK, editors. Medicinal Chemistry with Pharmaceutical Product Development. New Jersey: Apple Academic Press, 2019.

29. Mahapatra DK, Bharti SK, Asati V. Recent advancements in the Pharmacotherapeutic Perspectives of some chalcone scaffold containing natural compounds as potential Anti-virals. In: Mahapatra DK, Aguilar CN, Haghi AK, editors. Natural Products Pharmacology and Phytochemicals for Health Care: Methods and Principles in Medicinal Chemistry. New Jersey: Apple Academic Press, 2020.

30. Mahapatra DK, Bharti SK, Asati V. Chalcone (1,3-diphenyl-2-propene-1-one) scaffold bearing natural compounds as nitric oxide inhibitors: Promising anti-edema agents. In: Mahapatra DK, Aguilar CN, Haghi AK, editors. Applied Pharmaceutical Practice and Nutraceuticals: Natural Product Development. New Jersey: Apple Academic Press, 2020. Available at: https://www.taylorfrancis.com/chapters/edit/10.1201/9781003054894-1/chalcone-1-3-diphenyl-2-propene-1-one-scaffold-bearing-natural-compounds-nitric-oxide-inhibitors-promising-antiedema-agents-debarshi-kar-mahapatra-sanjay-kumar-bharti-vivek-asati

31. Chen, R. M., Hu, L. H., An, T. Y., Li, J., & Shen, Q., (2002). Natural PTP1B Inhibitors from Broussonetia papyrifera. Bioorganic and Medicinal Chemistry Letters, 12, 3387–3390.

32. Hoang, D. M., Ngoc, T. M., Da, N. T., Ha, D. T., Kim, Y. H., Luon, H. V., et al., (2009). Protein tyrosine phosphatase 1B inhibitors isolated from Morus bombycis. Bioorganic and Medicinal Chemistry Letters, 19, 6759–6761.

33. Zhang, L. B., Lei, C., Gao, L. X., Li, J. Y., Li, J., & Hou, A. J., (2016). Isoprenylated flavonoids with PTP1B inhibition from macaranga denticulata. Natural Products and Bioprospecting, 6, 25–30.

34. Na, M. K., Jang, J., Njamen, D., Mbafor, J. T., Fomum, Z. T., Kim, B. Y., et al., (2006). Protein tyrosine phosphatase-1b inhibitory activity of isoprenylated flavonoids isolated from erythrina mildbraedii. Journal of Natural Products, 69, 1572–1576.

35. Lei, C., Zhang, L. B., Yang, J., Gao, L. X., Li, J. Y., Li, J., et al., (2016). Macdenti chalcone, a unique polycyclic dimeric chalcone from macaranga denticulata. Tetrahedron Letters, 57, 5475–5478.

36. Yoon, G., Lee, W., Ki, S., & Cheon, S. H., (2009). Inhibitory effect of chalcones and their derivatives from Glycyrrhiza inflate on protein tyrosine phosphatase 1B. Bioorganic and Medicinal Chemistry Letters, 19, 5155–5157.

37. Park, S. J., Choe, Y. G., Kim, J. H., Chang, K. T., Lee, H. S., & Lee, D. S., (2016). Isoliquiritigenin impairs insulin signaling and adipocyte differentiation through the inhibition of protein-tyrosine phosphatase 1B oxidation in 3T3-L1 preadipocytes. Food and Chemical Toxicology, 93, 5–12.

38. Li, J. L., Gao, L. X., Meng, F. W., Tang, C. L., Zhang, R. J., Li, J. Y., & Zhao, W. M., (2015). PTP1B inhibitors from stems of angelica keiskei (Ashitaba). Bioorganic and Medicinal Chemistry Letters, 25, 2028–2032.

39. Ha MT, Seong SH, Nguyen TD, Cho WK, Ah KJ, Ma JY, Woo MH, Choi JS, Min BS. Chalcone derivatives from the root bark of Morus alba L. act as inhibitors of PTP1B and α-glucosidase. Phytochemistry. 2018;155:114-25.

40. Ren L, Li LZ, Huang J, Huang LZ, Li JH, Li YM, Tang SY. New compounds from the seeds of Psoralea corylifolia with their protein tyrosine phosphatase 1B inhibitory activity. Journal of Asian natural products research. 2019:1-6.