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Original Research Article

Structure-Activity Relationship Among the Antibacterial Pterocarpans from African Erythrina Species: A Review

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ABSTRACT

The genus Erythrina, a folkloric medicinal plant found in many tropical regions of the world, has yielded many flavonoids, including isoflavonoids of diverse structures. Some African Erythrina species have been investigated, and many have been found to contain isoflavonoids belonging to the sub-class pterocarpans which have displayed structural variations and interesting antibacterial activities. In this review, the structures and antibacterial activities of 14 pterocarpans reported in the literature from 8 African Erythrina species have been collated and subjected to structure-activity relationship (SAR) analysis to establish the best structural characteristics that enhance their antibacterial activities. The Structure-activity relationship (SAR) showed that their antibacterial activity against Gram-positive bacteria typified by *Staphylococcus aureus*, and the acid-fast organisms represented by *Mycobacterium smegmatis*, depends on the substitution pattern of the prenyl and hydroxyl groups on the two aromatic rings of the pterocarpan nucleus as well as the planarity of the pterocarpan molecule. Also, the high lipophilicity of the molecule provided by the presence of the prenyl groups enhances their antibacterial activity. Consequently, among the pterocarpans and indeed those from the African Erythrina species, 3,9-dihydroxypterocarpan (MIC=1.56 µg/mL), erycristagallin (MIC=3.13 µg/mL) and erythrabyssin II (MIC=3.12ug/mL) possess the best structural requirements for antibacterial activity against *Staphylococcus aureus* and *Mycobacterium smegmatis*. This review will guide the development of new antibacterial agents based on the pterocarpan framework.

Keywords: African Erythrina species, pterocarpans, antibacterial activities, structure-activity-relationship

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Introduction

It has been estimated that over 80% of the world population, particularly in developing countries, depend on medicinal herbs for their healthcare delivery system.[1] It has also been reported that the overall botanical and plant-based drug market in 2015 was valued at $25.6 billion with the potential to increase to $62 billion annually with increased popularity. Thus, large drug manufacturing companies in Europe and the USA have plant-derived compounds in their drug development pipelines because they are believed to be safer than synthetic, have efficacy against certain diseases, have flexibility in their accessibility, and preparation, and can be used with lower development costs.[2]

Species belonging to the genus *Erythrina* have long been known to play important roles in ethnomedicine, particularly in managing infectious diseases. Consequently, they have been subjected to chemical and biological activity screening for some decades for their chemical constituents[3,4] and bioactivities.[5-7] It has been reported that the genus Erythrina contains about 110 species of trees and herbs which have yielded 155 phytoconstituents from 15 species, and that *E. submbrans* and *E. variegata* contain the highest number.[6]

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More recently, investigations have been shifted to neutral components which have been found to possess biological activities.[6-9] Among the *Erythrina* species so far studied are 8 African medicinal plants, including *E. abyssinica*,[10] *E. x bidwilll*,[11] *E. burana*,[12] *E. crista-galli*,[13,14] *E. oriotricha*,[15] *E. mildbraedii*,[9,16,17] *E. sigmoidea*[18] and *E.* variegate.[19,20] Some of the neutral components isolated from the above plants included isoflavones belonging to the sub-class pterocarpans which displayed extensive structural variation and interesting *in vitro* antibacterial activity against *Staphylococcus aureus*. The pterocarpan scaffold (Figure 1) has the benzofuran-benzopyran moiety and compounds possessing it are known to be natural lead molecules with many pharmacological characteristics, including anticancer, antimicrobial, antimalarial, and antioxidant. Thus, they are good candidates for drug development.[2]

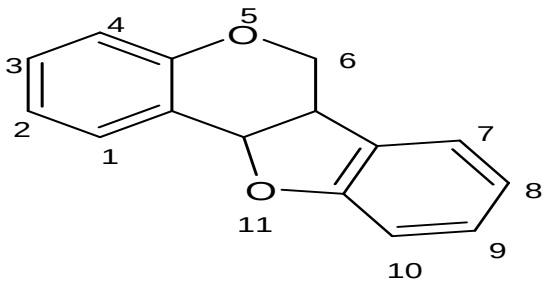

Figure 1: Pterocarpan Scaffold

In this review, 14 pterocarpans from African Erythrina species reported to possess antibacterial activity against *Staphylococcus aureus* and *Mycobacterium smegmatis* were assembled and subjected to structure-activity relationship analysis. It has been established that structure-activity relationship evaluation of bioactive compounds is important in

drug development as it relates a chemical entity to its biological activity by determining the functional group responsible for the target activity.[21,22] One of the approaches to achieving this is to embark on structural modification of a lead compound by synthetically transforming it through the introduction of various functional groups. Recently, some researchers explored SAR studies to develop drug leads for various ailments such as infections, cancer, and diabetes.[23-25] On the other hand, one or more plants can synthesise a family of compounds with diverse structural features that can be used to study structure-activity relationship as has been achieved for some flavanones and flavones, which has been one of the very few SAR studies on naturally-occurring compounds.[26] While SAR studies on natural flavonoids have been reported, no studies have so far been reported for isoflavonoids, particularly for the pterocarpan sub-class. The pterocarpans form the second largest group of isoflavonoids and their synthesis involving a tetracyclic framework has not been common.[27] The extensive structural variation displayed by the 14 antibacterial pterocarpans isolated from 8 African Erythrina species has provided a great opportunity to analyse their structure-activity relationship for future use of the pterocarpan framework for the development of new antibiotics. This is the focus of this paper, particularly as about 50% of the pterocarpans were obtained in our laboratories.[9,16,17]

Materials and Methods

There were no physical materials involved in this study, but some software applications were used in the methodology to generate data as described below.

Literature on sources of antibacterial *Erythrina* species was obtained using Google Scholar search engine which is a common and reliable academic search tool. The search was done generally on the genus *Erythrina* and after a careful study those from African environment and their pterocarpan constituents were identified in terms of countries of origin, chemical structures and antibacterial activities. The nature of substituents on the carbons 1, 2, 3, 4, 7, 8, 9, and 10 of the aromatic rings A and B of the pterocarpan scafold was closely studied and was found to generate enough structural variants for a review on structure-activity relationship.

The structures of the antibacterial pterocarpans were drawn using Advanced Chemistry Development's ACD/ChemSketch Freeware bundle toolkit (2022-2.3 version) by Chemist Isaac Asimov. It was downloaded on February 29, 2024, and was updated last on 23rd April, 2020.

Results and Discussion

A survey of the literature revealed that among the large number of species belonging to the plant genus Erythrina so far investigated for chemical constituents and antibacterial activity, 8 species from the African environment have been studied, and they yielded apart from other compounds, 14 isoflavonoids belonging to the pterocarpan sub-class (Tables 1). The pterocarpans coincidentally displayed selective antibacterial activity against *Staphylococcus aureus* and *Mycobacterium smegmatis* as well as interesting structural diversity to warrant their structure-activity relationship (SAR) analysis to determine the structural features that support their antibacterial activity. For this purpose, Table 2 was produced from available data to show the structures of the pterocarpans, with particular reference to the substitution patterns on the aromatic rings A and B, and the corresponding activities in MIC against *Staphylococcus aureus*, a Gram-positive pathogen associated with SDI and other infections 28 and *Mycobacterium smegmatis*, a nonpathogenic and fast growing species of the genus Mycobacterium, which provides a good candidate for Mycobacterial research on T.B. infection in man.[29]

The Structure-activity-relationship (SAR) among the African antibacterial pterocarpans against *Staphylococcus aureus* and *Mycobacterium smegmatis* is presented in Table 2. Analysis of the results in Table 2 shows that the pterocarpans erythrabyssin II (2), erycristagallin (13), and 3,9-dihydroxypterocarpan (14) are the most active with MICs of 3.12, 3.13 and 1.56 µg/mL, respectively, against *Staphylococcus aureus* when compared to streptomycin which exhibited MIC value of 50 µg/mL. Also, against *M. smegmatis* erythrabyssin II (2) displayed the highest activity at MIC of 0.78 µg/mL compared to streptomycin which recorded a MIC of 1.25 µg/mL. Sandwicensin (4), however, has no activity against any of the two organisms. At the same time, the other pterocarpans showed activity between 6.25 and 100 ug/mL against *Staphylococcus aureus* and between 6.25 and 25ug/mL against *Mycobacterium smegmatis*.

Careful examination of the structures of the pterocarpans (Figures 2-15) along with the substitution patterns shown in Table 2 revealed some important structural requirements for their antibacterial activity characteristics. One such structural feature is the presence of prenyl and hydroxyl groups on the aromatic rings A and B of the pterocarpanoid system. From Table 2, all the pterocarpans except sandwicensin (4) which lacks a free hydroxyl group on aromatic ring B and a prenyl group on ring A displayed antibacterial activity, suggesting that the two groups promote activity. The pterocarpans possessing the two groups on both rings display very appreciable activity. In contrast, those with these groups on either of the rings or lack the prenyl group by forming the chromene moiety exhibit decreased or no activity. Thus, erythrabyssin II (2), erycristin (3), and erybraedins A (5) and B (6), respectively, showed significant activity against both *Staphylococcus aureus* and *Mycobacterium smegmatis*. On the other hand, the activity of erybraedin D (8), erybraedin E (9), and isoneorautenol (10), was considerably lower. On the other hand, Sandwicensin (4), which lacks a prenyl group on ring A and has a blocked C-9 hydroxyl group in the B-ring has appreciable activity. This suggests that an overall lipophilic character is an important requirement for antibacterial activity against Gram-positive bacteria such as *Staphylococcus aureus.*[30] Based on the activity of erythrabyssin II (2), erybraedins A (5) and C (7), respectively, it appears that the substitution pattern on each of the aromatic rings is an important contributory factor to the degree of activity of the pterocarpans. Thus, a C-2 prenyl, C-3 OH substitution pattern on aromatic ring A, and a C-9 OH, C-10 prenyl substitution pattern on the B ring favour antibacterial activity. Consequently, erythrabyssin II, (2) and erycristagallin, (14), have greater activity than erybraedin A (5), which in turn shows greater activity than erybraedin C (7). The exact role of the hydroxyl group is not understood, but its importance for the antibacterial activity of some flavonoids has been reported.[31,32] The prenyl group on the other hand, increases the lipophilic character of the pterocarpans as in flavonoids[26] and thereby increases their ability to permeate the Gram-positive bacteria such as *S. aureus* which are known to have low cell wall lipid content.[26,31,32] Thus, pterocarpans with only one or no prenyl group show low antibacterial activity against *S. aureus*. This explains why the pterocarpans are generally inactive against Gram-negative bacteria with high cell wall lipid content. Being highly soluble in the cell wall they become trapped and therefore incapable of permeating the organism.

There is also a marked difference between the activity of erybraedin B (6), and erybraedin D (8), against *S. aureus* and *M. smegmatis* and between that of phaseollin (11) and phaseollidin (12). Both compounds (6) and (8) have the hydroxyl and prenyl groups on the B ring converted to a chromene moiety. However, compound (5) with the chromene C-31-C-41 double bond planar with the aromatic ring-B displays greater activity than compound (8) in which the C-31-C-41 double bond is not in plane with the aromatic ring. The planarity requirement which promotes effective conjugation may also account for the marked difference in the activity of phaseolin (11) and phaseollidin (12) against *S. aureus*. Thus, in chromene-bearing pterocarpans, the planarity of the C-31-C41 double bond with the aromatic B-ring seems to be an important factor. This is in good agreement with some reports for flavonoids.[31,32]

Conclusion

This review is the first structure-activity relationship analysis for the pterocarpans and has revealed some important structural characteristics that favour their antibacterial activity. They include the presence of hydroxyl and prenyl groups on the aromatic rings A and B, the substitution patterns on the rings, and the planarity of the molecules. The pterocarpans are generally active against Gram-positive bacteria

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because of their high lipophilic character enhanced by the presence of the prenyl group. The analysis has provided a base for the synthesis of novel antibacterial compounds based on the pterocarpan framework for specific purposes. Antibacterial agents based on the pterocarpan framework may be useful in medicine as drugs, and as disinfectants in the home, since they possess varying degrees of activity.

Conflict of Interest

The authors declare that there was no conflict of interest.

Authors' Declaration

The authors hereby declare that the works presented in this article are original and that any liability for claims relating to the content of this article will be borne by them.

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Table 1: African *Erythrina* species and their antibacterial pterocarpan constituents

African Erythrina Species	Antibacterial Pterocarpan Constituents	Country Location	References
E. abyssinica	Cristacarpin, erythrabyssin II, phaseollin, Phaseollidin	Angola, Sudan, Ethiopia, Burundi, Kenya, Malawi, Rwanda, Tanzania, Uganda, Zaire, Zambia, Mozambique, Zimbabwe, Mauritius	10
E. x bidwilli	Erythrabyssin II	Tanzania	11
E. burana	Cristacarpin	Ethiopia, Kenya	12
E. crista-galli	Phaseollidin, cristacarpin, 3,9-dihydroxy-pterocarpan, erycristagallin, erythrabyssin II, Sandwicensin, erycristin	Egypt, Ethiopia, Kenya, Mozambique, Rwanda, Sudan, Tanzania, Uganda, Zimbabwe	13,14
E. eriotricha	Erybraedin A,, C, D,E , isoneorautenol,	Cameroon	15
E. mildbraedii,	Erybraedin A, B, C, erythrabyssin II, isoneorautenol, erybraedin D, E.	Cameroon, Ghana, Nigeria, Guinea, Ivory Coast, Liberia, Sierra Leone, Togo, Togo, Uganda, Zaire	9,16,17
E. sigmoidea	Phaseollidin	Cameroon, Chad, Nigeria, Guinea, Ivory Coast, Mali, Senegal, Sudan, Togo	18
E. variegata	Erythrabyssin II, erycristagallin, phaseollidin, phaseollin	Egypt, Nigeria, Sao Tome, Principe, Senegal, Sudan, Tanzania, Uganda	19,20

Table 2: Substitution pattern and antibacterial activity of pterocarpans against *Staphylococcus* aureus(Sa) and *Mycobacterium smegmatis*(Ms)

Pterocarpans	Substituents on Aromatic Rings								MIC(µg/mL	
	1	2	3	4	7	8	9	10	Sa	Ms
Erythrabyssin-II 2	H	Prenyl	OH	H	H	H	OH	Prenyl	3.12	0.78
Erycristin 3	H	Prenyl	OH	H	H	H	OCH_3	Prenyl	6.25	6.25
Sandwecensin 4	H	H	OH	H	H	H	OCH_3	Prenyl	-	-
Erybraedin-A 5	H	H	OH	Prenyl	H	H	OH	Prenyl	12.5	6.25

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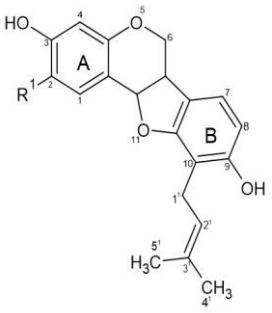
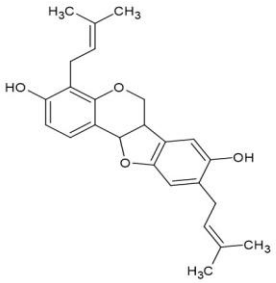
Erybraedin-B 6	H	H	OH	Prenyl	H	H	Chromene		12.5	12.5
Erybraedin-C 7	H	H	OH	Prenyl	H	Prenyl	OH	H	12.5	25.0
Erybraedin-D 8	H	H	OH	Prenyl	H	chromene		H	100.0	-
Erybraedin-E 9	H	Furan		H	H	H	OH	Prenyl	25.0	25.0
Isoneurautenol 10	H	H	OH	H	H	chromene		H	25.0	-
Isoneurautenol 11	H	H	OH	H	H	H	Chromene		12.5	-
Phaseollidin 12	H	H	OH	H	H	H	OH	Prenyl	50.0	ND
Erycristagallin 13	H	Prenyl	OH	H	H	H	OH	Prenyl	3.13	ND
3,9-Dihydroxy-pterocarpan 14	H	H	OH	H	H	H	OH	H	1.56	ND
Cristacarpin 15	H	H	OH	H	H	H	OH	Prenyl	1.56	1.25
Streptomycin SO_4									5.0	

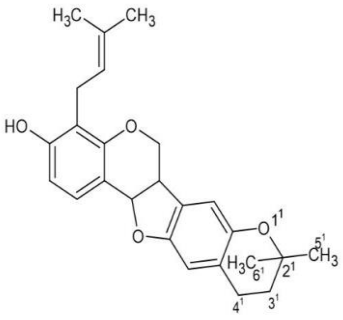
(-) inactive at 100 μg/mL concentration; ND=Not determine



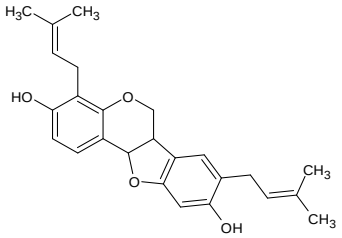
(2)R=H, R^1=prenyl, Erythrabyssin II
(3)R=CH_3, R^1=prenyl, Erycristin
(4)R=CH_3,R^1=H , Sandwecensin



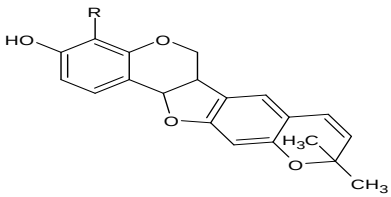
(5) Erybraedin A



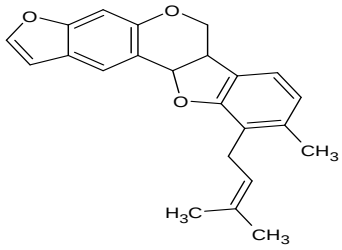
(6) Erybraedin B



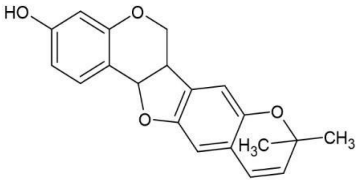
(7) Erybraedin C



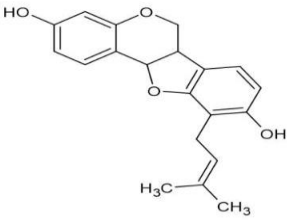
(8) R=prenyl, Erybraedin D
(10) R=H, Isoneurautenol



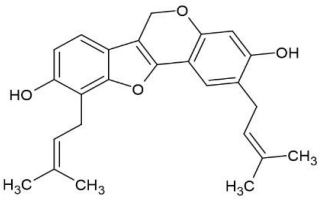
(9)Erybaedin E



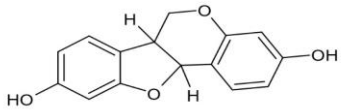
(11**)** Phaseollin



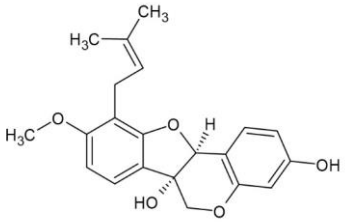
(12**)** Phaseollidin



(13**)** Erycristagallin



(14**)** 3,9-Dihydroxypterocarpan



(15**)** Cristacarpin

Figures 2-15: Structures of pterocarpans from African Erythrina species

References

1. Nontokozo ZM and Mthokozisi BCS. Herbal Medicine. Builders, FP. (Ed.); Publishers: IntechOpen 2019. doi: 10.5772/intechopen.69412.
2. Chelliah S, Brian CJ, Sandhya P, Daniel M, Romasamy T. Pterocarpan scaffold: A natural lead molecule with diverse pharmacological properties. Eur. J. of Med. Chem. 2017; 128:219-236.
3. Aparna K, Munit S, Nuvneet, Munish S. Ethnomedicinal, phytochemical, therapeutical and pharmacological review of the genus Erythrina. Int .J. of Bot. Stud. 2020; 5(6):642-648.
4. Douglas FR, Blegelmeyer R, Toson NSB, Dreschi RR, Moreno PRH, Henriques AT. The genus Erythrina L. A review of its alkaloids, preclinical and clinical studies. Phytother Res. 2019; 33(5):1258-1276.
5. Nouran MF, Eman A, Mohamed E, Abdel NS. A comprehensive review on flavonoids biological activities of Erythrina plant species. J. of Ind. Crops Prod. 2018; 123: 500-538. https://doi.org/10.1016/j.indcrop.2018.06.028.
6. Soto-Hernandez R, Garda-Mateos R, Mguei-Chavez RS, Kite G, Martinez-Vazquez M and Ramos-Valdivia AC. Bioactive compounds in phytomedicine. In: Erythrina, a potential source of chemicals from the neotropics. Iraj Rascool (Ed). 2012; www.intechopen.com.
7. Anjum A, Sultan MZ, Ferdosh S, Islam MK, Rashid MA, Nahar L and Sarkar SD. Flavonoid, pterocarpans, and steroid from *Erythrina fusca* Lour growing in Bangladesh: isolation and antimicrobial and free-radical scavenging activity. J. Med. Plants 2021; 20 (79):37-46.
8. Rahmawati R, Hartai YW, Latip JB and Herlina T. An overview of techniques and strategies for isolation of flavonoids from the genus Erythrina. J. of Separt. Sci. 2023; 46(12). https://doi.org/10.1002/jssc.202200800.
9. Njamen D. Anti-inflammatory activity of erycristagallin, a pterocarpene from *Erythrina mildbraedii*. Eur. J. of Pharmacol. 2003; 468(1):67-74.
10. Machumi F, Bojase-Moleta G, Mapitse R, Masesane I, and Majinda RRT. Radical scavenging -flavonoids from *Erythrina abyssinica*. Nat. Prod. Comm. 2006; 1(4):287-292.
11. Inuma M, Tanaka T, Mizuno M, Yamamoto H, Kobayashi Y and Yonemori S. Phenolic compounds of *Erythrina x bidwilli* and their activity against oral microbial organisms. Chem. and Pharm. Bull. 1992; 40:2749-2752.
12. Dagne E, Gunatilaka AA and Kingston DGI.. Two bioactive pterocarpans from *Erythrina bunana*. J. of Nat. Prod.1993; 56:1831-1834.
13. Ingham JJ and Markham KR. Identification of the Erythrina phytoalexin, cristacarpin, and a note on the charility of other 6a-hydroxypterocarpans. Phytochem. 1980;19:1203-1209.
14. Mitscher LA, Gollapudi SR, Gerlach DC, Drake SD, Veliz EA and Ward JA.. Erycristin, a new antimicrobial from *Erythrina crista-galli*. Phytochem. 1988; 27:381-385.
15. Nkengfack AE, Vouffo TW, Vardamides JC, Kouam J, Fomum ZT, Meyer M, and Steiner O. Phenolic metabolites from Erythrina species. Phytochemistry. 1997;46:573-578.
16. Mitscher LA, Drake S, Gollapudi SR and Okwute SK. A modern look at folkloric use of anti-infective agents. J. of Nat. Prod. 1987;50:1025-1046.
17. Mitscher LA, Okwute SK.,Gollapudi SR, Drake S and Avona E. Antimicrobial pterocarpans of Nigerian *Erythrina mildbraedii*. Phytochem. 1988; 27:3449-3452.
18. Nkengfack AE, Vouffo TW, Fomum ZT, Meyer M, Bergendoff T and Steiner O. Prenylated isoflavanone from
19. the roots of *Erythrina sigmoidea*. Phytochemistry 1994; 38:1047-1051.
20. Deshpande VH, Pendse AD and Pendse R. Erythrinins A, B and C, three new isoflavones from the bark of Erythrina variegata. Ind. J. of Chem. 1977; 158:205-207.
21. Telikepalli H, Gollapudi SR, Kashavarz-Shokri A, Velazouez L, Sandman. RA, Veliz EA, Rao KVJ, Madhavi S, Mitscher LA. Isoflavonoids and a cinnamyl phenol from root extracts of *Erythrina variegata*. Phytochem. 1990; 29:2005-2007.
22. Wikipedia. en-wikipedia.org/wiki/structure-activity-relationship; retrieved ,21st July, 2024; last updated 7th April,2024.
23. Ahmad A, Elisha IL, van Vuuren S, and Viljoen A. Volatile phenolics: A comprehensive review of the anti-infective

24. properties of an important class of essential oil constituents. Phytochem. 2021; 90: 112864. doi.org/10.1016/j.phytochem2021.112864.
25. Mohamed AT and Amr E. Pederins, mycalamides, onnamides, and theopederins: Distinctive polyketide families with intriguing therapeutic potentialities. Curr. Res. in Biotechnol. 2023; 6:100145.
26. Rameshwar SC, Sachin DS, Jaya P, Ambhore SRC, Sanjay BB. Quinazoline: an update on the current status against convulsions. J.of Mol. Struct. 2022;1248:131384.
27. https:doi.org/10.1016/j.molstruc.2021.131384;
28. Lijuan W, Xiaonan Z, Jun Z, Menglin Y, Jinbo Y, Peiju Q. The therapeutic effects of marine sulfated polysaccharides on diabetic nephropathy. Int. J. of Biol. Macromol. 2024; 261, Part 1: 129269.https://doi.org/10.1016/j.ijibomac2024.129269.
29. Echeverria J, Opazo J, Mendoza L, Urzua A and Wilkens M. Structure-activity relationships of selected antibacterial natural flavones and flavanones of Chilean flora. Mol. 2017: 1-15.
30. Leticia JG, Carmen HC, Mariam AC, Manuel MD, and Igracio, RG. Synthesis of pterocarpans. Nat. Prod. Comm. 2011; 6(4):537-554.
31. Taylor TA, Unakal, CG. *Staphylococcus aureus* infection. In: StatPearls[Internet]. StatPearls Publishing 2024, Updated July 17, 2023; https;//ncbi.nlm.gov/books/NBK441868/.
32. Sparks IL, Derbyshire KM, Jacobs WR Jr, Morita YS. *Mycobacterium smegmatis*: The Vanguard of Mycobacterial Research. J Bacteriol. 2023;205(1):e0033722. doi: 10.1128/jb.00337-22. Epub.
33. Kyung-Min P, Seon JL, Hyungjong YYP, Ho-Sup J, Keesung K, Chang JL, and Pahn-Shick C. Hydrophilic and lipophilic characteristics of non-fatty acid moieties: significant factors affecting the antibacterial activity of lauric acid esters. 2018; 27(2):401-409. https://doi.org/10.1007/s/0068018-0353-x.
34. Akihisa M, Chikao N, Nobuyasu E, Shinkichi T. Antibacterial activity and mode of action of plant flavonoids against *Proteus vulgaris* and *Staphylococcus aureus*. Phytochem. 1987; 26(8):2231-2234.
35. Xie Y, Yang W, Tang F, Chen X, Ren L. Antibacterial activities of flavonoids: Structure-
36. activity relationship and mechanism. Curr. Med Chem. 2015; 22(1):132-149.