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Research Article

Biological Activities of Gossypitrin: A review

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Abstract

Flavonoids pigments, one of more numerous groups widely distributed of natural constituents, sometimes known as antoxantins, frequently appear in chemical literature, especially in the last 50 years, and they are characterized by their antioxidant activity, free radical scavenging capacity, coronary heart disease prevention, hepatoprotective, anti-inflammatory, and anticancer activities, while some flavonoids exhibit potential antiviral activities. Gossypitrin (G7G) the main chemical compound present in the petals of the flowers of *Taliparitielatum* (Sw.) that grow in Cuba was tested to determine its biological activities. This chemical compound is a flavonoid glycoside which is a gossypetin derivative with a sugar moiety attached in C7. flavonoids [12]. This review deals with the structural aspects of G7G and their protective roles against many human diseases.

Keywords: Flavonoids; Taliparitiri; Gossypitrin; Human Health; COVID-19

Introduction

Flavonoids consist of a large group of polyphenolic compounds having a benzo-γ-pyrone structure with one or more hydroxyl groups attached in different positions. Due to the aromatic nature of those phenolic compounds they show an intense absorption in UV region of spectra. Flavonoids are divided into different classes, such as anthocyanins, chalcones, dihydrochalcones, dihydroflavonols, flavanols, flavanones, flavones, flavonols and isoflavonoids [1,2].

Flavonoids present great biological potential, including antioxidant and antiviral activities, and some are mentioned as potential substances against Covid-19. They have been used to treat a number of health problems, such as infections, sinusitis, gastritis, inflammations, and flu. Several other flavonoid-producing sources are used worldwide, the absorption, metabolism, and pharmacokinetics of flavonoids have been intensively investigated, and glucuronide and sulfates can be highlighted as important metabolite products in this process [2,3].

Structurally speaking, all classes of flavonoids are arranged under a system C_6-C_3-C_6 in which two aromatic rings (A and B) are joined by one unit of three carbons that could be or not another ring, called ring C. Most of them, appear in nature as aglycone, but, some others are glycosylated in different positions, principally in C3' and C4', C3, C7, etc. (Figure 1) [4,5].

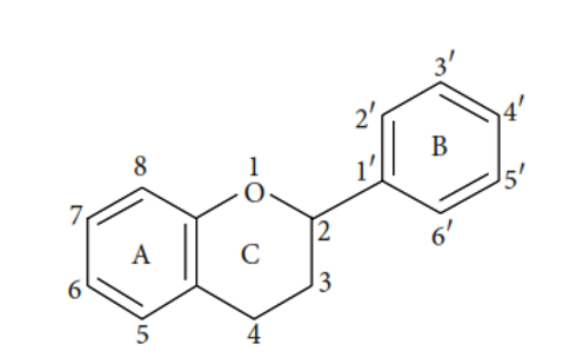

Figure 1: Basic flavonoid structure.

This review highlights the structural features of gossypitrin, the main component of the petals of the flowers from *Talipariti elatum* (Sw.) in Cuba and their beneficial roles in human health.

History

Gossypitrin was first taken out in 1916 by Parking from the flower of *Gossypium herbaceum* [7], later the compound was detected in different *Equisetum* species [8,9] and identified in yellow petals of *Papaver nudicaule* [10], and Drosera peltata (shield sundew), a specie distributed in India and Southeast Asia [11].

The active molecule is present in *Hibiscus sabdariffa* L. [12-14], and in *Hibiscus tiliaceus* [15]. In Cuba, it was isolated and characterized by the first time in 1999, using 1,2-dimethoxyethane as solvent and the full flowers of *Hibiscus elatus* Sw. (common name: Majagua) [16].

Our research team isolated and characterized the chemical compound from the red petals of the flower of *Talipariti elatum* (Sw.) (ancient name *Hibiscus elatus* Sw.) after extraction with EtOH at 95 % in Soxhlet apparatus during 20 hours. Cuba and Jamaica are the most important countries were the tree is present, although in some others islands in the Caribbean Sea the plant was adopted (Martinica, Puerto Rico, Panama, etc.) [17].

Chemistry of gossypitrin

Gossypitrin is a glucoside flavonoid that have a glucose moiety attached in its skeleton in C7 and belongs to flavonol subgroup because the presence of an OH group in C3 [18] and hydroxylated in positions 5, 8, 3' and 4' [19] (Figure 2).

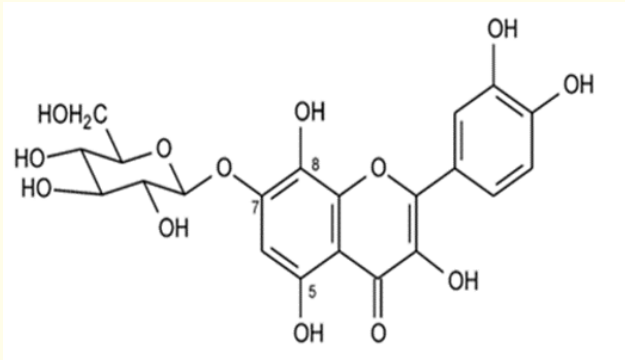

Figure 2: Chemical structure of gossypitrin.

Spectral characteristics of gossypitrin

UV spectroscopy of flavonoids are usually determined in methanolic solutions. The spectrum consists in two major absorption bands: Band I (320-385nm) represents the B ring absorption, while Band II (250-285 nm) corresponds to the A ring absorption. Gossypitrin shows a maximum absorption at 382 nm, with a free hydroxyl group at 3, supporting by the existence of a band bellow 350 nm, and cathecolic groups in ring B (substitution in 3', 4') because a band at 278 nm and an inflection at 257 nm, and three oxygenated positions on ring A [20,21] (Figure 3).

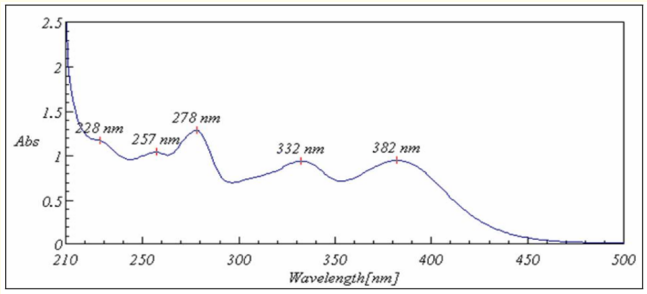

Figure 3: UV Spectrum of gossypitrin.

IR spectrums showed typical presence of associated hydroxyl groups, alkyl groups, carbonyl group and aromatic rings due to

different bands at 3 375 cm^{-1}; 3 000-2 980 cm^{-1}; 1 656 cm; 1 610, 1 600, 1 569 and 1 519 cm^{-1}, respectively. Stretching C-O band is around 1200 cm^{-1}. According with these results and data in literature we suggested that this compound is a flavonol [22,23] (Figure 4).

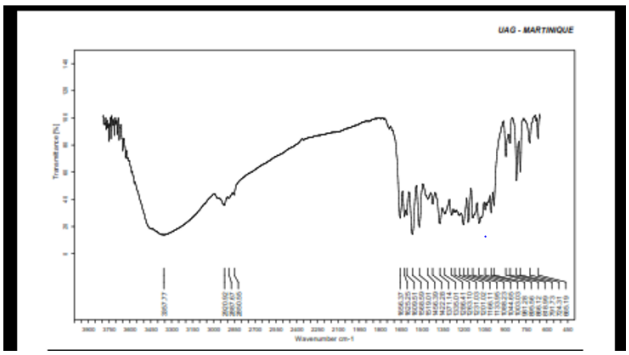

Figure 4: IR Spectrum of gossypitrin.

LC-MS of gossypitrin in both ion scan modes (positive and negative) shows a molecular mass of 481 m/z and 479 m/z, respectively. Successive losses of 162 u indicate the loss of the glucose moiety given a molecular peak of 318 u that belongs to gossypetin aglycon [24] (Figure 5).

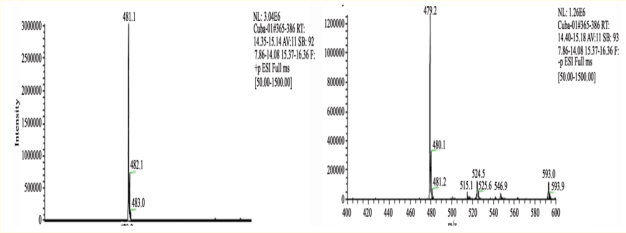

Figure 5: MS Spectrum of gossypitrin in (+) and (-) ion modes.

^{1}H NMR spectrum of this flavonoid derivative showed four proton signals in the aromatic region at 8.07 ppm (C2'), 6.99 ppm (C5'), 7.92 ppm (C6'), consistent with a gossypetin derivative. Observed chemical shift value of proton 6-H (δ = 6.25 ppm) and carbon 6-C (δ =97.98 ppm) confirmed the presence of Hydroxyquinol (ring A). Glucose molecule attached in carbon 7 show proton signals at 4.83 ppm (C1''), 3.44-3.34 ppm (C2''; C3''; C4''; C5'') and 3.76-3.63 ppm (C6''). Hydroxyl groups show signals at 9.39 ppm (3-OH), 11.90 ppm (5-OH), 8.60 ppm (8-OH), 9.42 ppm (3'-OH) and 9.35 ppm (4'-OH) [25]. Signal corresponding to 7-OH disappear due to the presence of a glucose moiety (Figure 6).

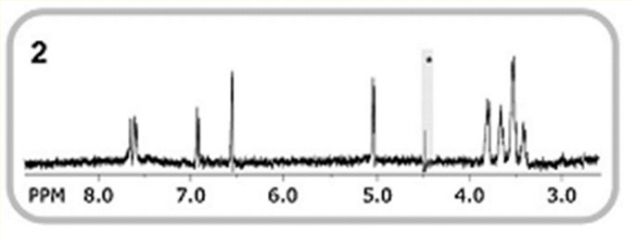

Figure 6: ^{1}H NMR of gossypitrin.

^{13}C NMR spectrum shows signals between 60.15-101.84 ppm corresponding to the carbons of the sugar moiety; ten quaternary carbons and 15 signals belonging to a flavonol. Unequivocally, signal at 98. 05 ppm belongs to C6 [26].

Biological activities of gossypitrin

Antioxidant activity

The antioxidant activity of flavonoids depends upon the arrangement of functional groups about the nuclear structure. The flavonoid heterocycle contributes to antioxidant activity by permitting conjugation between the aromatic rings and the presence of a free 3-OH. Due to this intramolecular hydrogen bonding, the influence of a 3-OH is enhanced by the presence of a 3', 4'-catechol, elucidating the potent antioxidant activity of flavan-3-ols and flavon-3-ols that possess the latter feature. The B ring hydroxyl configuration is the most significant determinant of scavenging of ROS and RNS because it donates hydrogen and an electron to hydroxyl, peroxyl, and peroxynitrite radicals, stabilizing them and giving rise to a relatively stable flavonoids radical [27].

In this sense, gossypitrin after 12 different tests showed antioxidant activities in all assays, being the best results against HOCL, and $ONOO^{\bullet}$ (Table 1). TEAC assay allow us to infer that this flavo-

noid glucoside is between the 10 best natural compounds in the world in front of the 30 principal chemical components using in international marked according to Rice-Evans and Miller, 1996 [28,29].

No.	Assay	Method	Standard		Gossypitrin
1	DPPH	Blois, 1958	Quercetin	8.05 µg/mL	18.376 µg/mL
2	TEAC	Re., *et al*. 1999 (m)	Quercetin	4.56 mM	2.14 mM
3	Reducing Power	Oyaizu, 1986	Quercetin	24.09 µg/mL	68.95 µg/mL
4	$O_2^{\cdot-}$	Fernandes., *et al*. 2003	Trolox	1.83 ± 0.09 x 10^3 µM	28.9 ± 3.2 µM
5	HOCl	Yildiz., *et al*. 2004	Lipoic acid	2.37 ± 0.13 µM	1.17 ± 0.19 µM
6	ROO·	Fernandes., *et al*. 2004	Fluorescein	1	2.68 ± 0.22 µM
7	·NO	Nagata., *et al*. 1999	Rutin	0.52 ± 0.02 µM	1.68 ± 0.12 µM
8	ONOO· (1)	Kooy., *et al*. 1994	Ebselen	2.51 ± 0.09 µM	1.09 ± 0.07 µM
9	ONOO· (2)	Kooy., *et al*. 1994	Ebselen	16.0 ± 1.9 µM	2.12 ± 0.15 µM
10	H_2O_2	Costa., *et al*. 2005	Lucigenin		(*)
11	HO·	Oosthuizen & Greyling, 2001	Luminol		(*)
12	Inhibit. XO	Fernandes., *et al*. 1999	Allopurinol	5.11 ± 0.19 µM	52.8 ± 2.2 µM

Table 1: IC_{50} values caluclated from the scavenging activity of gossypitrin sample against DPPH, ABTS, reducing power, ROS, RNS and engymatic assays.

(*) No activity was detected in the H_2O_2 and HO assay up to the sample concentration of 100mM (1* and 2*) within and without the presence of NaHcCO3, respectively.

Because of their capacity to chelate metal ions (iron, copper, etc.), flavonoids also inhibit free radical generation. Gossypitrin have the capacity to chelate trace elements like Fe^{3+} and Cu^{2+}. Both of them are good prooxidant agents in human body [30-32]. Trace metals bind at specific positions of different rings of flavonoid structures [33]. The binding sites are shown in figure 7, demonstrated by our research team by UV, IR and MS experiments.

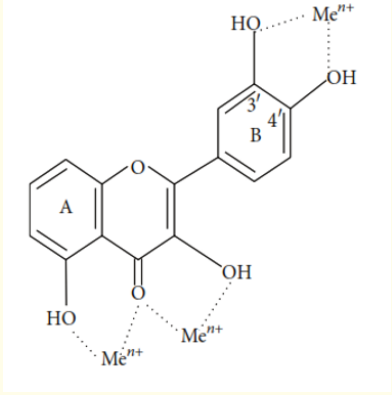

Figure 7: Binding sites for trace metals where Me^{n+} indicates metal ions.

Antibacterial and Antifungal activities

In the antimicrobial activity evaluation were used 26 strains of bacteria (Gram + and Gram -), where only one was from clinical origin, and 13 strains of fungus of *Candida* genus (all of them collection strains). Table 2 shows only the best results obtained in from of bacteria and fungus with gossypitrin.

Gossypitrin has an antibacterial effect of 53, 85 %, being positive its inhibition effect in front of 14 of the 26 strains of evaluated microorganisms. Only in front of two of 13 strains of fungus had a good effect (15, 38%) [34].

Neuroprotective effect

Gossypitrin showed a potent intrinsic antioxidant capacity evidenced by low IC_{50} and EC_{50} values for DPPH/ABTS/malondialdehyde and ferric reducing power, respectively. Gossypitrin significantly increased the survival of PC_{12} against KCN. The levels of GSH and the SOD and CAT enzymes activities were restored. G7G reduced the level of lipid peroxidation and showed values of antioxidant effects higher than rutin using as positive control. The neu-

Strains (bacteria)	ATCC	Screening	MIC (mg/mL)	MBC (mg/mL)
Staphylococcus epidermidis	12228	+	5	5
Proteus vulgaris	13315	+	10	5
Klebsiella pneumoniae	13833	+	10	10
Staphylococcus aureus	33862	+	20	20
Staphylococcus aureus	clinical	+	20	20
Escherichia coli	35150	+	20	20
Shigella flexneri	12022	+	30	30
Strains (fungus)			**MIC (mg/mL)**	**MIF (mg/mL)**
Candida subtilis		+	20	20
Candida albicans	10231	+	20	20

Table 2: Antimicrobial activities of gossypitrin.

Name	Type	Rank	Violation
Nictoflorin	P	1	3
Quercitrin	P	2	2
Luteolin-7-Glucoside	P	3	2
Gossypetin-3'-*O*-Glucoside	P	4	2
Gossypetin-7-*O*-Glucoside	P	5	2
Gossypetin-8-Glucoside	P	6	2
Lopinavir	D	7	1
Astragalin	P	8	2
Gossypetin-3-Glucoside	P	9	2
Nelfinavir	D	10	1
Piceid	P	11	1
Remdesivir	D	12	2
Kaempferol	P	13	0
Quercetin	P	14	0
Natural Ligand		15	2

Table 3: Rank of compounds regard to Lupinski's rules violation.

roprotective potential of gossypitrin against hypoxic cell damage is probably associated to its antioxidant effects [35-37].

Anti SARS-COV-2 activity. molecular docking

Severe Acute Respiratory Syndrome (SARS) was the first new infectious disease identified in the twenty-first century. Very few data are available on the clinical use of medicinal plants to prevent or cure COVID-19. Gossypitrin, among another three Gossypetin derivatives and some drugs and medicinal plants molecules was tested for the first time by molecular docking, to determine its possibilities to use as putative inhibitors of SARS-COV-2 [38,39]. Taking into account the Lupinski's rule were calculated the violations by each compound [40]. Authors are showing here only the 15 first places reached by the experiments where are included the four gossypetin derivatives and some others chemical compounds (Table 3) [41].

Figure 8 shows the molecular interactions between the active site of 3CLpro and G7G. Gossypetin-7-*O*-Glucoside (G7G) presents the most bonds to the protein. G7G links with probably new and non-critical residues: Thr24, Thr26, Thr45, Cys44, Ser46 and His163.

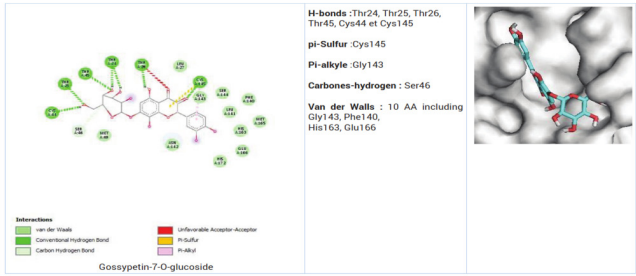

Figure 8: Binding residues and docking poses of G7G (gossypitrin).

Conclusion

Gossypitrin, the main chemical component found out in ethanolic extracts of the petals of *T. elatum* (Sw.) in Cuba appear promising. Its antioxidant, antimicrobial, quelating and neuroprotective activities suggest this flavonoid glucoside as a good candidate for the prevention of several diseases. The study should be supplemented with in vivo experiments to refine the therapeutic propos-

als. Gossypitrin as well as other glycoside flavonoids, are present in a large number of therapeutic medicinal plants and are often consumed in the form of herbal teas. These compounds are vital in diets and are of great interest due their biological activities. For this reason, their absorption, metabolism, toxicity, and pharmacokinetics should be intensively investigated. Regarding these studies, all those flavonoid glucosides, are deglycosylated prior to being absorbed into circulation and then conjugated mainly with glucoronate and sulfate, these being the main forms in plasma. Gossypitrin can be propose as good tropical natural compounds candidate that should be further investigated to prevent or treat COVID-19, taking into account the good results reached by the use of molecular docking displayed here as an active agent against 3CLpro of SARS-CoV-2.

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