Guttiferones: an insight into occurrence, biosynthesis, and their broad spectrum of pharmacological activities

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Highlights

- Guttiferones are bioactive molecules found in the *Clusiaceae* family of plants.
- Guttiferones belong to the polyisoprenylated benzophenone class.
- There are at least 20 types of guttiferones.
- Guttiferones act as an anti-inflammatory, antioxidant, antitumor and antimicrobial agent.
- Little is known about guttiferones toxicity.

Abstract: Guttiferones belong to the polyisoprenylated benzophenone, a class of compounds, a very restricted group of natural plant products, especially in the Clusiaceae family. They are commonly found in bark, stem, leaves, and fruits of plants of the genus *Garcinia* and *Symphonia*. Guttiferones have the following classifications according to their chemical structure: A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, Q, R, S, and T. All of them have received growing attention due to its multiple biological activities. This review provides a first comprehensive approach to plant sources, phytochemical profile, specific pharmacological effects, and mechanisms of guttiferones already described. Studies indicate a broad spectrum of pharmacological activities, such as: anti-inflammatory, immunomodulatory, antioxidant, antitumor, antiparasitic, antiviral, and antimicrobial. Despite the low toxicity of these

compounds in healthy cells, there is a lack of studies in the literature related to toxicity in general. Given their beneficial effects, guttiferones are expected to be great potential drug candidates for treating cancer and infectious and transmissible diseases. However, further studies are needed to elucidate their toxicity, specific molecular mechanisms and targets, and to perform more in-depth pharmacokinetic studies. This review highlights chemical properties, biological characteristics, and mechanisms of action so far, offering a broad view of the subject and perspectives for the future of guttiferones in therapeutics.

Keywords: Benzophenone; Guttiferones; Synthesis; Effects; Mechanisms.

Abbreviations:

ABTS: Diammonium 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonate)
AMP: ampicillin
AP-1: Activator protein 1
Bax: Bcl-2-associated X protein
Bcl-2: B-cell lymphoma two protein
BPAP: Bicyclic Polyprenylated Acylphloroglucinol
CCCP: Carbonyl cyanide m-chlorophenylhydrazone
DPPH: 2,2-diphenyl-1-picryl-hydrazyl-hydrate
HAT: histone acetyltransferase enzyme
HepG2: human hepatocellular carcinoma-derived
HIV: Human immunodeficiency virus
HPLC: High-Performance Liquid Chromatography
HSCCC: High-Speed Counter-Current Chromatography
HUVEC: Human umbilical vein endothelial cells
IC_{50}: inhibitory concentration
IFN-γ: interferon - γ
IL-18: interleukin – 18
IL-1β: interleukin - 1β
IL-6: interleukin - 6
LPS: Lipopolysaccharide
MAPK: Mitogen-Activated Protein Kinase
MC: minimum concentration
MHC: major histocompatibility complex

MMP: mitochondrial membrane potential
MS: mass spectrometry
mTOR: mammalian target of rapamycin
MTT: (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide)
NF-κB: nuclear factor – κB
NK: Natural Killer cells
NMR: Nuclear Magnetic Resonance
NSAID: Non-steroidal anti-inflammatory drug
NTD: Neglected tropical diseases
ORAC: Oxygen Radical Absorbance Capacity
PFN1: profilin 1
PPAP: Polycyclic polyprenylated acylphloroglucinol
ROS: reactive hydrogen species
STAT-1: Signal transducer and activator of transcription 1
TBARS: Thiobarbituric Acid Reactive Substances
TEAC: Trolox Equivalent Antioxidant Capacity
TLR: Toll-like receptor
TNF-α: tumor necrosis factor – α
VCAM-1: vascular cell adhesion molecule 1

1. Introduction

Plants with medicinal properties have recently been of great interest to science and the pharmaceutical industry. About 73% of drugs produced by this industry have substances of natural origin in their compositions (Shedoeva et al., 2019). This trend will persist in the coming years due to the plethora of recent discoveries concerning new compounds from plants like the genus *Garcinia*, that belong to the Clusiaceae family.

Clusiaceae is a family of plants found in tropical and subtropical regions as shrubs and trees. Their fruits, barks, leaves, roots, flowers, latex, and branches are candidates for study to identify bioactive or therapeutic compounds contained in them, based on their use by the local populations endemic to the regions in which they grow for the treatment of diseases (Angami et al., 2021).

By isolating molecules such as garcinol, isogarcinol, xanthocymol, isoxanthocymol and different isoforms of guttiferones found abundant in *Garcinia* genus plants, an understanding

of the therapeutic properties of each compound has developed. Guttiferones, in particular, have a variety of medicinal effects that also apply to their 20 identified isoforms named from A to T. Anti-inflammatory (Dzoyem et al., 2015), antitumor (Lin et al., 2019), antioxidant (Bagattoli et al., 2016), antiparasitic (Ngouela et al., 2006), antiviral (Martins et al., 2009) and immunomodulatory (Coste et al., 2020) are some examples of bioactive properties discovered in isolated guttiferones.

Literature on guttiferones has been emerging only in recent years, and there is still a lack of consensus on an agreed nomenclature. Due to the wide variety of therapeutic actions of such molecules, accompanied by the extensive research on the chemical structure and pharmacological activities of guttiferones, there is an urgent need to organize the knowledge obtained so far to facilitate future research on the subject. This review systematically summarizes and comprehensively analyzes primary information on molecular structure, plant sources, assays, biological activities, and action mechanism of guttiferones reported so far, offering a broad view of the subject and perspectives for the future of guttiferones in therapeutics.

2. Search Methodology

To provide novel insights and support the pre-clinical or clinical use of Guttiferones, we summarized an extensive search for relevant articles published in the English language between 2000 and 2021 conducted in the following databases: PubMed, Scopus, ISI web of Cochrane Database of Systematic Reviews, Science Direct, LILACS, Google Scholar, REAXYS, Chemical Abstracts, EMBASE and Medline. We have used "guttiferones" either alone or combined with "red propolis," "polyisoprenylated benzophenone" or "garcinia" as keywords for literature searches. Initially, 322 research papers were selected from with the above search strategy. Duplicate articles were excluded and articles with similar results and studies using extracts or fractions enriched with guttiferones were also excluded. Only 81 articles about pharmacological effects were finally included after reading the titles, abstracts, and whole papers.

3. Occurrence, isolation, and chemical properties of guttiferones

Most isolated guttiferones have come from species from the genus *Garcinia* (Clusiaceae). However the molecules were also reported on *Symphonia*, *Calophyllum*, *Allanblackia* (Acuna et al., 2009), and *Clusia* (Baggett, Mazzola & Kennelly et al., 2005) plant species, all of them from the Clusiaceae family (Table 1). Intensive research on Clusiaceae

plants has been conducted, and the accomplishment that guttiferones were the main compounds made the name "Guttiferae" commonly used in replacement. However, according to the Angiosperm Phylogeny Group classification (2016), the accepted name of the family is Clusiaceae, not Guttiferae (Chase et al., 2016).

Table 1: Plant sources of guttiferones

Plant species	Used part	Extract	Type	Isolated content (mg/g)	Reference
Garcinia brasiliensis	Seeds	Ethanol	Guttiferone A	8.57	(Martins et al., 2011)
Garcinia gardneriana	Seeds	Ethyl acetate	Guttiferone A	227.27	(Rodrigues et al., 2021)
Garcinia intermedia (cited as *Rheedia edulis*)	Seeds	Methanol	Guttiferone A	0.38	(Acuña et al., 2010)
Symphonia globulifera	Seeds	Methanol–Dichloromethane (1:1)	Guttiferone A	22.5	(Ngouela et al., 2006)
Symphonia globulifera	Seeds	Methanol	Guttiferone A	41.15	(Cottet et al., 2015)
Symphonia globulifera	Seeds	Methanol–Dichloromethane (1:1)	Guttiferone A	60.86	(Fromentin et al., 2013)
Symphonia pauciflora	Leaves and fruits	Ethanol	Guttiferone A	0.9	(Pana et al., 2010)
Symphonia pauciflora	Leaves and fruits	Ethanol	Guttiferone I	1.2	(Pana et al., 2010)
Garcinia oblongifolia	Bark	Ethyl acetate	Guttiferone B	15.15	(Hamed et al., 2006)
Garcinia esculenta	Twigs and leaves	Ethanol	Guttiferone F	6.01	(Zheng et al., 2021)

Garcinia xanthochymus	Fruit pulp	Methanol	Guttiferone H	0.12	(Baggett et al., 2005)
Garcinia smeathmanii	Root Bark	Hexane	Guttiferone I	2.22	(Lannang et al., 2006)
Garcinia gummi-gutta (cited as *Garcinia cambogia*)	Fruits	Ethanol	Guttiferone K	62.50	(Kolodziejczyk et al., 2009)
Garcinia madruno (cited as *Rheedia acuminata*)	Stem bark	Dichloromethane	Guttiferone K	13.11	(Almanza et al., 2011)
Garcinia planchonii	Fruit pericarp	*n*-Hexane	Guttiferone Q	0.79	(Trinh et al., 2014)
Garcinia macrophylla	Twigs and stems	Ethyl acetate-Methanol	Guttiferone A	5 mg	(Williams et al., 2003)
Garcinia macrophylla	Twigs and stems	Ethyl acetate-Methanol	Guttiferone G	30 mg	(Williams et al., 2003)
Garcinia punctata	Stems	Methanol	Guttiferone E	215 mg	(Kuete et al., 2013)
Garcinia nujiangensis	Twigs	Acetone	Guttiferone F	Not reported	(Tang et al., 2015)
Garcinia xanthochymus	Fruits	Methanol	Guttiferone A	Not reported	(Einbond et al., 2013)
Garcinia intermedia	Fruits	Methanol	Guttiferone J	Not reported	(Einbond et al., 2013)
Garcinia cochinchinensis	Fruits	Methanol	Guttiferone Q-S	Not reported	(Nguyen et al., 2011)
Garcinia cochinchinensis	Fruits	Methanol	Guttiferone I	Not reported	(Nguyen et al., 2011)
Garcinia cochinchinensis	Fruits	Methanol	Guttiferone R	Not reported	(Nguyen et al., 2011)
Garcinia livingstonei	Stems and fruits	Dichloromethane, ethyl acetate and methanol	Guttiferone A	Not reported	(Mulholland et al., 2013)
Symphonia globulifera	Not reported	Not reported	Guttiferone A	Not reported	(Duval et al., 2020)

Garcinia brasiliensis	Fruits	Seeds	Guttiferone A	Not reported	(Barros et al., 2015)
Garcinia brasiliensis	Fruits	Hexane, ethyl acetate and ethanol	Guttiferone A	Not reported	(Pereira et al., 2010)
Symphonia globulifera	Leaves	Methanol	Guttiferone A	12 mg	(Lenta et al., 2007)
Allanblackia gabonensis (cited as *Allanblackia monticola*)	Fruits	Hexane-Methanol	Guttiferone F	21 mg	(Lenta et al., 2007)
Clusia rosea	Flowers	Not reported	Guttiferone A	Not reported	(Monzote et al., 2015)
Garcinia intermedia	Leaves	Dichlorometane-methanol (1:1)	Guttiferone A	720 mg	(Abe et al., 2004)
Garcinia × *guacopary* (cited as *Garcinia achachairu*)	Seeds	Methanolic	Guttiferone A	660 mg	(Niero et al., 2012)
Garcinia gummi-gutta (cited as *Garcinia cambogia*)	Fruits	Ethanolic	Guttiferone M	4.5 mg	(Masullo et al., 2014)
Garcinia gummi-gutta (cited as *Garcinia cambogia*)	Fruits	Ethanolic	Guttiferone K	7.5 mg	(Masullo et al., 2014)
Garcinia punctata	Barks	Methanolic	Guttiferone E	215 mg	(Dzoyem et al., 2015)
Garcinia yunnanensis	Fruits	Acetone	Guttiferone K	3.0 g	(Zhang et al., 2020)
Garcinia aristata	Fruits	n-hexane	Guttiferone A	0.8 g	(Pardo-Andreu et al., 2011)
Garcinia livingstonei	Fruits	Methanolic	Guttiferone A	18.8 mg	(Yang et al., 2010)
Garcinia livingstonei	Fruits	Methanolic	Guttiferone K	20.0 mg	(Yang et al., 2010)
Garcinia livingstonei	Fruits	Methanolic	Guttiferone E	Not reported	(Yang et al., 2010)

Garcinia multiflora	Twigs	Methanolic	Guttiferone E	113 mg	(Liu et al., 2010)
Garcinia multiflora	Twigs	n-hexane-acetone	Guttiferone F	303 mg	(Liu et al., 2010)
Garcinia schomburgkiana	Wood	n-hexane	Guttiferone K	14.5 mg	(Boonyong et al., 2017)
Garcinia xanthochymus	Fruits	Methanolic	Guttiferone H	38 mg	(Baggett et al., 2005)
Garcinia xanthochymus	Fruits	Methanolic	Guttiferone E	22.4 mg	(Baggett et al., 2005)
Garcinia calcicola (cited as *Rheedia calcicola*)	Fruits	Methanolic	Guttiferone K	20 mg	(Cao et al., 2007)
Garcinia bancana	Barks	Methanolic	Guttiferone F	3.6 mg	(Coste et al., 2020)
Garcinia bancana	Barks	Methanolic	GX (Guttiferone F and Xanthocymol as a mixture)	8.7 mg	(Coste et al., 2020)
Garcinia × *guacopary* (cited as *Garcinia achachairu*)	Seeds	Methanol	Guttiferone A	660 mg	(Terrazas et al., 2013)
Garcinia aristata	Fruits	n-hexane	Guttiferone A	Not reported	(Figueredo et al., 2011)
Garcinia brasiliensis	Seeds	Methanol	Guttiferone A	0.51 g	(Martins et al., 2009)

Guttiferones belong to a group of secondary metabolites named polycyclic polyprenylated acylphloroglucinols (PPAPs), characterized by the presence of oxygenated acylphloroglucinol-derived cores with isoprenyl or geranyl side chains. The biosynthetic pathway of PPAPs in plants is the mixed mevalonate/methylerythritol phosphate and polyketide biosynthetic route, where the condensation of three malonyl-CoA units and one acyl-CoA unit forms a polyketide that cyclizes into acylphloroglucinol; this core can be polyprenlated and submitted to cyclization processes to form diverse skeletons (Phang et al., 2020; Yang et al., 2018; Yang et al., 2015).

According to the relative position of the acyl group on the phloroglucinol core, PPAPs were divided into three groups, namely: bicyclic polyprenylated acylphloroglucinols (BPAPs); caged PPAPs; and metabolites derived directly from monocyclic polyprenylated acylphloroglucinols (MPAPs) (Yang et al., 2018; Yang et al., 2015). BPAPs represent 60% of all the PPAPs and are subdivided into type A, B, and seco-BPAPs, guttiferones belonging to type B. This subclass main features are acyl groups located at the C-3 position, in most cases, with an *endo*-C-7 group (Yang et al., 2018).

According to the current literature, twenty guttiferone isoforms have been identified, denominated from A-T (Figure 1, 2, and Table 2). A recent literature review made by Yang et al. (2018) noted that some guttiferones were given two different names, as in the case of (+)-guttiferone G and oblongifolin C, gutifferone J and garciyunnannin A, guttiferone Q and cowanone, each pair having the same molecular structure. In other cases, two different structures received the same name, as happened to "guttiferone I" and "13-deoxy-guttiferone J"; as well as "guttiferone O" and the "oxy-oblongifolin A" (Yang et al., 2018).

Figure 1. Chemical structures of guttiferones A, B, C, D, E, F, G, H and I

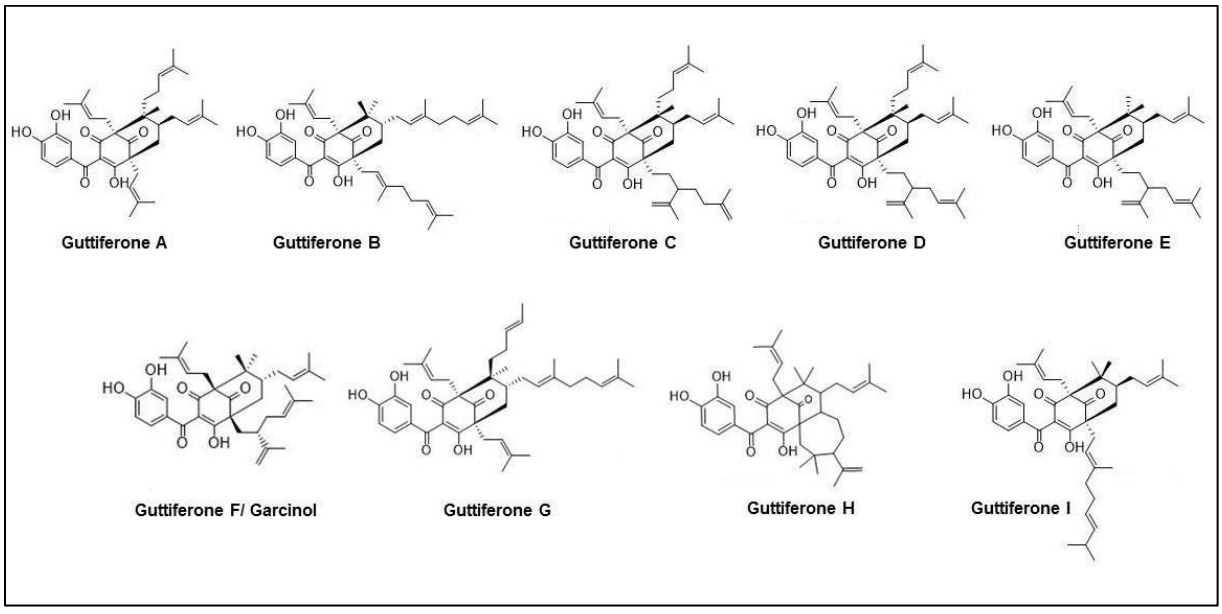

Figure 2. Molecular structures of guttiferones N (1), M (2), O (3), J (4), K (5), P (6), (+)-G (7), L (8), Q (9), T (10), S (11) and R (12).

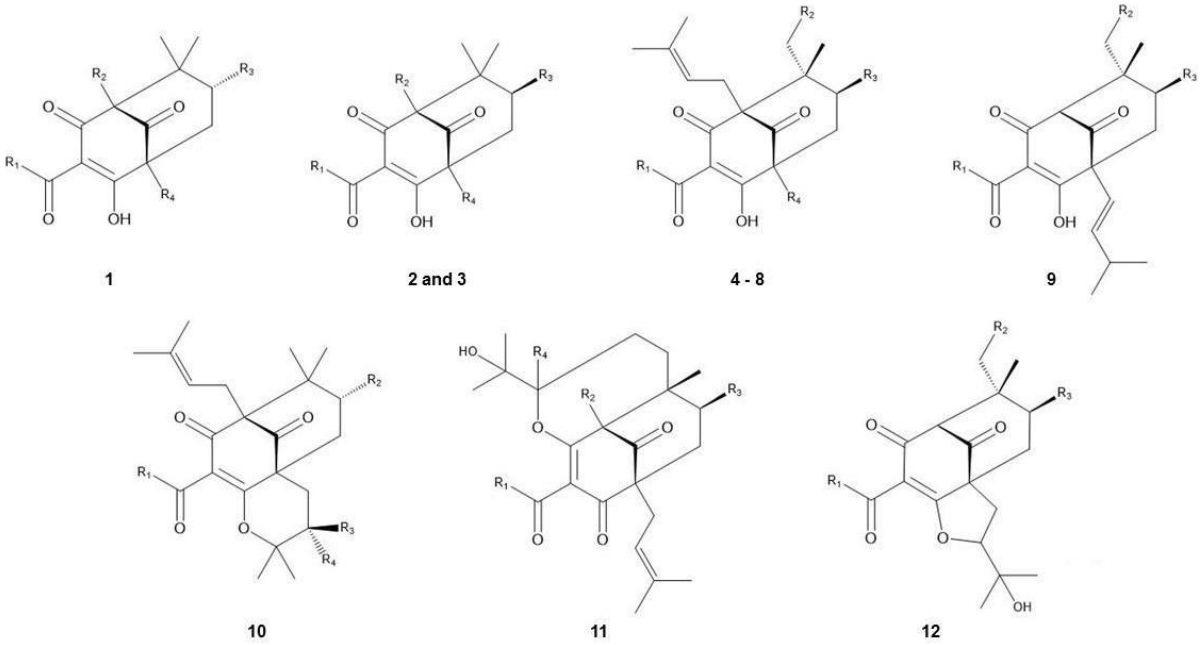

Table 2. R group components of guttiferones.

no.	type	R groups
1	N	R1 = 3-(HO)C_6H_4; R2, R3 = prenyl; R4 = genaryl
2	M	R1 = 3-4(HO)$_2C_6H_3$; R2, R3 = prenyl; R4 = genaryl
3	O	R1 = 3-4(HO)$_2C_6H_3$; R2, R4 = geranyl; R3 = prenyl
4	J	R1 = 3-(HO)C_6H_4; R2, R3, R4 = prenyl
5	K	R1 = 3,4-(HO)$_2C_6H_3$; R2, R3, R4 = prenyl
6	P	R1 = 3,4-(HO)$_2C_6H_3$; R2, R3 = prenyl, R4 = geranyl
7	(+)-G?	R1 = 3,4-(HO)$_2C_6H_3$; R2, R4 = prenyl, R3 = geranyl
8	L	R1 = 3,4,6-(HO)$_3C_6H_2$; R2, R3, R4 = prenyl
9	Q	R1 = Ph; R2, R3 = prenyl

10	T	R1 = 3,4-$(HO)_2C_6H_3$; R2 = $CH_2CH(OH)CMe=CH_2$; R3 = $CH_2CH_2CMe=CH_2$; R4 = H
11	S	R1 = Ph; R2, R4 = H; R3 = prenyl
12	R	R1 = Ph; R2, R3 = prenyl

Guttiferone F is a particular case of structural misassignment. The molecule was described as a 30-epimer of garcinol. However, by nuclear magnetic resonance (NMR), x-ray, and chemical transformation assays, it was determined that guttiferone F is actually garcinol (Zheng et al., 2021). Single-crystal x-ray diffraction analysis and other electronic circular dichroism (ECD) spectroscopy techniques commonly used to analyze compounds are insufficient to elucidate the absolute structures of garcinol derivatives, concluded Wang et al. (2021).

A step before elucidating the molecular structures of guttiferones is their isolation from plant material. For that, different chromatographic techniques have been used, such as silica gel column chromatography (Hamed et al., 2006), sometimes performed as successive passages with solvent alterations that improve the isolation of guttiferones from each type of extract (Ngouela et al., 2006).

Some PPAPs are isolated as mixtures, such as guttiferone E and its regioisomer xanthochymol, forming a complex named "GX." Li et al. (2017) reported the separation of this mixture using HPLC for the isolation of GX followed by HSCCC (High-Speed Counter-Current Chromatography). HPLC was performed with modifications of the solvent system, being *n*-hexane, methanol and water more efficient for the isolation of GX from (4:6:1) an ethanolic extract of *G. xanthochymus*.

The mixture of guttiferone E and xanthochymol was also a target for chemical transformation studies, such as the one made by Lin et al. (2019) aiming to increase its antitumor activity. In this study, GX was submitted to chemical transformation that resulted in four compounds. From those, a series of 40 analogs were obtained. At the time, it was the first report of PPAPs chemical transformation that resulted in new stable molecules, some presenting higher antitumor activity than the precursors, again highlighting the opportunity to create new drugs derived from guttiferones with potential biological activities (Lin et al., 2019).

Molecular modifications on specific sites of PPAPs are also a strategy to change their biological activities and phisico-chemical properties that might enhance their performance

when applied to living organisms. In the majority of the PPAP skeleton, three endocyclic stereocenters (C-1, C-5, and C-7) can be identified, and according to the configuration of these centers, the molecule can be *endo*- or *exo*- oriented, giving rise to distinct structures (Horeischi et al., 2014). However, in a small percentage of PPAPs, the C-6-atom also has a stereogenic center that can determine the orientation type of the substance. A C-6 side chain induction can have a strong influence not only on the molecule's orientation but also on its biological activity. Horeischi et al. (2014) performed a diastereoselective synthesis of guttiferone A by controlling the stereocenters and establishing a new one. With this conformational control, they synthesized two endo-type B of PPAPs: guttiferone A and 6-epi-guttiferone A, expanding the possibilities of creating PPAPs with specific conformations useful in determined situations for its biological activities, for example.

By modification of hydroxyl groups at positions C-13 and C-14 of guttiferone A that changed the lipophilicity of the molecule (and thus its affinity for targets), Dias and its collaborators (2012) investigated the antimicrobial action of the PPAP's semisynthetic derivatives. Guttiferone A is known for its antibacterial activity against gram-positive and gram-negative bacteria such as *Staphylococcus aureus* and *Proteus mirabilis*, respectively. The authors suggest that molecule modifications that altered lipophilicity resulted in higher antibacterial activity of compounds 13,14-di-methanesulfonyl-guttiferone-A, 13,14-di-chlorobenzoyl-guttiferone-A and 13,14-di-toluenesulphonyl-guttiferone-A against *S. aureus* and *Bacillus cereus* than the usual medication, chloramphenicol (Dias et al., 2012).

The complexity and diversity of guttiferones have been study through different analytical methods. Guttiferone A has been reported with a retention factor (Rf) value of 0.47 on silica gel plates, eluted with hexane-ethyl acetate 6:1: (v/v) and revealed with vanillin solution (Rodrigues et al., 2021). Thin layer chromatography (TLC) has also been used to monitored and isolated (on preparative mode) semisynthesis of guttiferone-A derivatives (Dias et al., 2012).

However, HPLC-UV is one of the most employed techniques for guttiferones analysis. Methods developed on reversed phase columns of different suppliers (150mm × 4.6mm, 5 µm), with a 254 nm detection and variances on the mobile phases, are the described by different papers. Guttiferones A-D from *S. globulifera* organs, were analyzed using a linear gradient elution method of acetonitrile and acidified water (Cottet et al., 2015). Methods for quantification of guttiferone A and other compounds from *G. gardneriana* seed extract, were developed with acetonitrile-distilled water-H_3PO_4 (4:1:0.025 v/v) as mobile phase (Rodrigues et al., 2021). Other methods quantified guttiferone A on *G. brasiliensis* seeds and fruit's

pericarp, using a mobile phase of methanol–acetic acid (pH 3.84; 0.001M) (40:60 v/v) (Martins et al., 2011). Mixtures of organic phases for the analysis of isomers as guttiferone E and xhanthochymol, were proposed to avoid coelution problems on C18 columns (Synergi Polar, 250 × 4.6 mm, 4 µm) (Li et al., 2017).

Other analytical techniques include mass spectra (MS), using electrospray ionization (ESI) mode (Lin et al., 2019; Zheng et al., 2021) and electrospray ionization-quadrupole-time of flight mass spectrometer (ESI-Q-TOF-MS) (Rodrigues et al., 2021); nuclear magnetic resonance (NMR) recorded with methanol-*d4* + 0.1% TFA (Li et al., 2017; Zheng et al., 2021); optical rotations at [α]20 (Cottet et al., 2015; Zheng et al., 2021) and IR Spectra on FT-IR instruments (Hamed et al., 2006; Rodrigues et al., 2021).

Therefore, with improving isolation techniques and molecular elucidation techniques, as well as a better understanding of the consequences of modifying certain parts of the guttiferone structure on its physico-chemical properties, a consensus on guttiferone naming and potential biological activities definition is not far.

4. Pharmacological activities of guttiferones

4.1 Antioxidant activity

Cell metabolism generates reactive oxygen species (ROS), also known as free radicals, which in excess may lead to deleterious oxidation of enzymes, lipids, proteins, and DNA resulting in membrane disruption and consequent cell death. This oxidative stress is present in many pathologies, such as degenerative diseases (Singh et al., 2021). Several natural compounds exert antioxidant activity by inactivating free radicals, being phenolic compounds the most recognized class of plant-derived molecules with antioxidant activity, guttiferones also added into this group (Bagattoli et al., 2016; Kolodziejczyk et al., 2009).

As shown in table 3, Guttiferone A, in an experiment performed by Ngouela et al. (2006), showed promising antioxidant activity with 89% of free radical inhibition, being higher than the positive control - caffeic acid - that presented only 58% of inhibition. Bagattoli et al. (2016) compared the antioxidant activity of the guttiferone with another natural product derived molecule, vitamin C, the results showing a similar range of activity for both. Guttiferone K tested by Almanza et al. (2011) was compared to quercetin but in this case, showed less antioxidant activity than the flavonoid. Guttiferones H and I were also submitted to antioxidant activity tests and presented IC_{50} of 64 µM (Baggett et al., 2005) and 26.8 µM (Lannang et al., 2006), respectively.

Table 3. Antioxidant, anti-inflammatory, immunomodulatory (MHC and VCAM), antiparasitic, antimicrobial effects and mechanisms of guttiferones in *in vitro* and *in vivo* assays.

Model	Assay	Substance	Dose/Concentration	Effect	Mechanisms	Reference
Antioxidant						
In vitro	DPPH assay	Guttiferone A	0.21 mg/mL	89 ± 0.5 % of inhibition	Radical scavenging	(Ngouela et al., 2006)
In vivo	DPPH and ABTS assay	Guttiferone A	1-300 mg/mL	CE_{50} 10.75 ± 27 µg/mL / CE_{50} 8.48 ± 1.46 µg/mL	Radical scavenging	(Bagattoli et al., 2016)
In vitro	ORAC assay	Guttiferone A	Not reported	404.0 ± 1.5 (mM TE/g/mL)	Radical scavenging	(Bagattoli et al., 2016)
In vitro	DPPH and ABTS assay	Guttiferone A	0.01-0.5 mM	IC_{50} 30.99 ± 0.56 µM / IC_{50} 12.53 ± 0.11 µM	Radical scavenging	(Acuña et al., 2010)
In vitro	DPPH assay	Guttiferone H	Not reported	IC_{50} 64 ± 2.1 µM	Radical scavenging	(Baggett et al., 2005)
In vitro	DPPH assay	Guttiferone I	1000 µM	92.3 % of scavenging activity and IC_{50} of 26.8 µM	Radical scavenging	(Lannang et al., 2006)
In vitro	DPPH and ABTS assay	Guttiferone J	0.01-0.5 mM	IC_{50} 466.07 ± 20.77 µM / IC_{50} 252.68 ± 14.77 µM	Radical scavenging	(Acuña et al., 2010)

In vivo	DPPH and ABTS assay	Guttiferone K	Not reported	IC_{50} 2.33 ± 0.05 µg/mL / IC_{50} 11.07 ± 0.11 µg/mL	Radical scavenging	(Almanza et al., 2011)
In vitro	TEAC assay	Guttiferone K	1 mM	2.5 of TEAC	Radical scavenging	(Almanza et al., 2011)
In vitro	ELISA (for the determination of TBARS in platelets)	Guttiferone K	10 and 25 µg/mL	Reduction of TBARS level about 50% and 40%, respectively	Inhibited the effect of peroxynitrite on platelet lipid peroxidation	(Kolodziejczyk et al., 2009)
In vitro	ELISA (for the detection of carbonyl groups in human platelet and plasma proteins)	Guttiferone K	25 µg/mL	25 µg/mL	Diminished the carbonyl group generation in blood platelet and plasma proteins	(Kolodziejczyk et al., 2009)
In vitro	TBARS (in plasma)	Guttiferone K	25 µg/mL	At the presence of peroxynitrite reached about 40% of plasma lipid peroxidation reduction	Inhibited the effect of peroxynitrite on plasma lipid peroxidation	(Kolodziejczyk et al., 2009)
In vitro	DPPH assay	Guttiferone K	Not reported	IC_{50} 68 ± 0.33 µM	Radical scavenging	(Baggett et al., 2005)
In vitro	DPPH and ABTS assay	Guttiferone M	0.01 - 0.5 mM	IC_{50} 38.32 ± 0.98 µM / IC_{50} 45.58 ± 2.00 µM	Radical scavenging	(Acuña et al., 2010)
In vitro	DPPH assay	Guttiferone Q	40 µg/mL	2.7 ± 0.2 of scavenging activity	Radical scavenging	(Trinh et al., 2014)

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Model	Assay	Substance	Dose/Concentration	Effect	Mechanisms	Reference
Anti-inflammatory						
In vitro - (RAW 264.7 cells)	Griess Reaction (NO production)	Guttiferone E	3.12 µg/mL	72.88 ± 2.47% of NO production inhibition	High cytotoxicity against RAW 264.7 cells	(Dzoyem et al., 2015)
			6.25 µg/mL	90.09 ± 3.52 % of NO production inhibition		

			12.5 µg/mL	94.55 ± 4.38 % of NO production inhibition		
			25 µg/mL	94.06 ± 5.87 % of NO production inhibition		
In vitro - (RAW 264.7 cell)	Ferrous oxidation-xylenol orange assay (LOX inhibition)	Guttiferone E	100 µg/mL	74.39 ± 5.09 % of LOX inhibition	LOX inhibition	(Dzoyem et al., 2015)
In vitro - (RAW 264.7 cell)	MTT assay (cell viability)	Guttiferone E	3.12 µg/mL	IC_{50} = 57.45 ± 1.33 µM	High cytotoxicity against RAW 264.7 cells	(Dzoyem et al., 2015)
			6.25 µg/mL	IC_{50} = 35.31 ± 1.19 µM		
			12.5 µg/mL	IC_{50} = 24.17 ± 0.62 µM		
			25 µg/mL	IC_{50} = 14.98 ± 0.48 µM		
			100 µg/mL	IC_{50} = 43.05 ± 1.59 µM		
In vitro - (MDA-MB-231 cell)	Electrophoretic mobility shift assay (EMSA)	Guttiferone K	10 µM	Inhibition of IFNγ-induced STAT-1 activation	Binding affinity between the compound and related cytokines	(Masullo et al., 2014)
			25 µM			
			50 µM			
		Guttiferone M	25 µM	Inhibition of IFNγ-induced STAT-1 activation	Binding affinity between the compound and related cytokines	(Masullo et al., 2014)
			50 µM			
In vitro - (INS-1E cell)	Electrophoretic mobility shift assay (EMSA)	Guttiferone K	25 µM	Inhibition of IFNγ-induced STAT-1 activation	Binding affinity between the compound and related cytokines	(Masullo et al., 2014)

In vitro - (RAW264.7 cell)	CCK-8 (cell viability)	Guttiferone K	20 μM	Safe relative cell viability percentage (close to 100%)	Weak inhibitory effect on cells viability	(Zhang et al., 2020)
In vitro - (RAW264.7 cell)	ELISA	Guttiferone K	10 μM	Regulation of Mtb-triggered uncontrolled inflammation	Inhibition of *Mycobacterium tuberculosis* -triggered IL-1β, TNF-α and IL-6 secretion	(Zhang et al., 2020)
In vitro - (RAW264.7 cell)	Western Blot	Guttiferone K	10 μM	Regulation of Mtb-triggered uncontrolled inflammation	Inhibition of iNOS, COX2, pro-IL-1β and NLRP3 (inflammasome) expression	(Zhang et al., 2020)
					Inhibition of p65 and IRAK-1 phosphorylation	
In vitro - (Primary macrophage)	Western Blot	Guttiferone K	10 μM	Regulation of Mtb-triggered uncontrolled inflammation	Inhibition of pro-IL-1β expression	(Zhang et al., 2020)

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Model	Assay	Substance	Dose/Concentration	Effect	Mechanisms	Reference
Antimicrobial						
In vitro – (S. agalactiae)	Minimal inhibitory concentration (MIC)	Guttiferone A	1 mg	MIC = 7.81 μg/mL	Synergistic antibacterial activities in combination with clavulanic acid and ampicillin, and strong binding to β-lactamase	(Maia et al., 2018)
In vitro – (S. uberis)				MIC = 15.62 μg/mL		
In vitro – (*S. aureus, B. cereus, S. typhimurium, C. parapsilosis, C. glabrata, C. neoformans*)	Inhibitory concentration of microbial growth 50% = IC_{50}	Guttiferone A	0.06 to 100 μg/mL	IC_{50} = 8.29 μmol/mL IC_{50} = 0.06 μmol/mL IC_{50} = 0.06 μmol/mL IC_{50} = 33.17 μmol/mL IC_{50} = 8.29 μmol/mL IC_{50} = 8.29 μmol/mL	Not reported	(Dias et al., 2012)

In vitro – *(C. krusei)*	Minimal inhibitory concentration (MIC)	Guttiferone A	0.117 to 100 µg/mL	MIC (1) = 7.50 µg/mL MIC (2) = 1.87 µg/mL	Synergistic antifungal activities in combination with fluconazole. MIC (1) = alone and MIC (2) = combined.	(de Carvalho et al., 2018)
In vitro – *(C. glabrata)*	Minimal inhibitory concentration (MIC)	Guttiferone A	0.117 to 100 µg/mL	MIC = 7.5 µg/mL	Not reported	(de Carvalho et al., 2018)
In vitro – (*E. coli*, *E. aerogenes*, *K. pneumoniae*)	Minimal inhibitory concentration (MIC)	Guttiferone BL	2 to 512 µg/mL	MIC = 512 µg/mL MIC = 256 µg/mL MIC = 512 µg/mL	Not reported	(Nganou et al., 2018)
In vitro – (*S. aereus*)	Inhibitory concentration of microbial growth 50% = IC_{50}	Guttiferone A	0.25 to 64 µg/mL	IC_{50} = 7.5 ± 0.8 µM	Not reported	(Monzote et al., 2011)
In vitro – (*C. freundii*, *E. cloaclae*, *P. vulgaris*, *B. megaterium*, *S. faecali*)	Minimal inhibitory concentration (MIC)	Guttiferone I	0.038 to 19.53 µg/mL	MIC =1.96 µM (Gram-positive), MIC = 0.98 µM (Gram-negative)	Not reported	(Kuete et al., 2007)
In vitro – (*S. aereus*, *B. cereus*)	Minimal inhibitory concentration (MIC)	Guttiferone A	Not reported	MIC = 2.4 µg/mL	Not reported	(Naldoni et al., 2009)

Model	Assay	Substance	Dose/Concentration	Effect	Mechanisms	Reference
Immunomodulatory effect on MHC and VCAM related molecules						
In vitro - (HUVEC cells)	MTT (Cytotoxic activity)	Guttiferone J	10 μM	More than 100% of cell viability	Protective effect of the guttiferone or nonspecific interferences on the metabolic pathway measure by MTT	(Rouger et al., 2016)
	ELISA (for VCAM-1 detection)			Immunosuppressive action by preventing leukocytes adhesion to the endothelium	Significant suppression of VCAM-1 expression	(Rouger et al., 2016)
	Immunostaining (for HLA-E detection)			Immunosuppressive action by preserving HLA-E levels close to its basal concentration	Inhibition of IFNγ-mediated HLA-E production	(Rouger et al., 2016)
In vitro - (HUVEC cells)	Flow cytometry (for MHC molecules detection)	Guttiferone J	10 μM	Immunosuppressive action by MHC molecules levels modulation	Inhibition of IFNγ-mediated production of MHC class II molecules	(Zhang et al., 2020)
	Flow cytometry (for VCAM-1 detection)			Immunosuppressive action by preventing leukocytes adhesion to the endothelium	Significant inhibition of VCAM-1 expression	(Zhang et al., 2020)
In vitro - (Human primary vascular endothelial cell)	MTT (Cytotoxic activity)	Guttiferone F	1 to 20 μM	No significant cytotoxic effect at concentrations equal or below 10 μM	Inhibition of HAT CBP/p300 activity and of IFNγ on MHC molecules	(Coste et al., 2020)
	Flow cytometry (for MHC molecules detection)		10 μM	Up to 75% of MHC molecules expression inhibition after treatment with IFNγ		
	qRT-PCR		10 μM	Significant decrease of HLA class I, HLA-E, β2M and tapasin levels		

	qRT-PCR		10 μM	Significant decrease of MICA and MICB		
	qRT-PCR		10 μM	Inhibition of STAT1 and SOCS1		
	qRT-PCR		10 μM	Reduction of CIITA and GATA2 mRNA levels		
In vitro - (Human primary vascular endothelial cell)	Western blot	Guttiferone F	10 μM	Inhibition of STAT1 phosphorylation	Regulatory effect of HAT CBP/p300 activity	(Coste et al., 2020)
				Inhibition of CBP (K1535)/p300 phosphorylation		

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Model	Assay	Substance	Dose/Concentration	Effect	Mechanisms	Reference
Antiparasitic						
In vivo - *(S. mansoni cercariae)*	Excretory System Activity	Guttiferone A	Not reported	ED_{50} = 21.8 μg/mL	Surface damage, causing immobility of the microorganism	(Barros et al., 2015)
			20.0 μg/mL	Harmful to the excretory system and to the tegument	The substrate of P-glycoprotein is prevented of leaving to the external environmental due the presence of guttiferone A	
			20 μg/mL	83.3% of worms mortality	Tegument damage	
			25 μg/mL	100% of worms mortality		
In vitro - (promatigote form of *L. amazonensi)*	Leishmanicidal activity	Guttiferone A	0.05 - 100.0 mg/mL	IC_{50} = 18.12 μg/mL	Molecular features that enhance a molecule's lipophilicity and biological activity	(Pereira et al., 2010)

In vitro - (amastigote form of *L. amazonensi)*	Leishmanicidal activity	Guttiferone A	0.05 - 100.0 mg/mL	IC_{50} = 2.93 µg/mL		
In vitro - (Murine peritoneal macrophage)	MTT assay (Cytotoxic activity)	Guttiferone A	0.05 - 100.0 mg/mL	IC_{50} = 10.71 µg/mL		
In vitro - (L. donovani amastigote form*)*	Leishmanicidal activity	Guttiferone A	Not reported	IC_{50} = 0.16 µM	Not reported	(Lenta et al., 2007)
	Leishmanicidal activity		0.8 µg/mL	82.1% of parasite growth inhibition		(Lenta et al., 2007)
	Leishmanicidal activity		4.8 µg/mL	98.3% of parasite growth inhibition		(Lenta et al., 2007)
	Leishmanicidal activity	Guttiferone F	0.8 µg/mL	58.2% of parasite growth inhibition	Inhibition of iNOS, COX2, p65, IRAK-1, IL-1β, NLRP3 expression	(Lenta et al., 2007)
	Leishmanicidal activity		4.8 µg/mL	98.2% of parasite growth inhibition	Inhibition of pro-IL-1β and NLRP3 expression	(Lenta et al., 2007)
	Leishmanicidal activity		Not reported	IC_{50} = 0.20 µM	Not reported	(Lenta et al., 2007)
In vitro - (L-6 cells)	Cytotoxicity assay	Guttiferone A	0.13 – 90 µg/mL	IC_{50} = 7.3 µM	Not reported	(Lenta et al., 2007)
		Guttiferone F		IC_{50} = 5.4 µM		(Lenta et al., 2007)
In vitro - (Acetylcholinesterase)	Cholinesterase inhibition assay	Guttiferone A	Not reported	IC_{50} = 0.88 ± 0.04 µM	Not reported	(Lenta et al., 2007)
In vitro (Acetylcholinesterase)		Guttiferone F	Not reported	IC_{50} = 0.95 ± 0.01 µM	Not reported	(Lenta et al., 2007)

In vitro - (Butyrylcholinesterase)		Guttiferone A	Not reported	IC_{50} = 2.77 ± 0.02 µM	Not reported	(Lenta et al., 2007)
In vitro - (Butyrylcholinesterase)		Guttiferone F	Not reported	IC_{50} = 3.50 ± 0.15 µM	Not reported	(Lenta et al., 2007)
In vitro - (*L. tarentolae* promastigote form)	Leishmanicidal activity	Guttiferone A	25 – 400 µM	IC_{50} = 6.2 ± 2.6 µM	Reduction of oxygen consumption that guttiferone A creates by interfering in the complex III activity	(Monzote et al, 2015)
In vitro - (Peritoneal macrophage)	MTT assay (cytotoxic activity)		Not reported	IC_{50} = 9.2 ± 0.9 µM	Not reported	(Monzote et al, 2015)
In vitro - (*L. tarentolae* promatigote form)	Oxygen consumption assay		>50 µM	IC_{50} = 163.8 ± 20.0µM (Moderate reduction of oxygen consumption)	Not reported	(Monzote et al, 2015)
In vitro - (*L. tarentolae* promatigote form)	JC-1 assay (mitochondrial membrane potential)		200 µM	Strong decrease in mitochondrial membrane potential	Not reported	(Monzote et al, 2015)
In vitro - (*T. cruzi* epismatigote form)	Trypanocidal activity	Guttiferone A	Not reported	MC_{100} = 60 µg/mL	Not reported	(Abe et al., 2004)
In vitro - (*T. cruzi* trypomastigote form)	Trypanocidal activity	Guttiferone A	Not reported	MC_{100} = 50 µg/mL	Not reported	(Abe et al., 2004)
In vitro - *(P. falciparum* W2 strain)	Antimalarial activity	Guttiferone A	10 mM	IC_{50} = 3.17 µM	Inhibition of the hemozoin formation	(Ngouela et al., 2006)

In vitro - (*P. falciparum* 3D7 strain)	^{3}H-hypoxanthine incorporation assay	Guttiferone A	0 – 50 μM	IC_{50} = 3.32 ± 0.45 μM	Not reported	(Duval et al., 2020)

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Model	Assay	Substance	Dose/Concentration	Effect	Mechanisms	Reference
Other pharmacological effects						
In vitro - (PCRCN and PC12 cells)	XTT assay (cell viability)	Guttiferone A	0.01 and 0.05 μM	Increase on Iron-overloaded cells viability (close to 100%)	The free radical scavenging activity enhances cells survival against iron-induced oxidative stress	(Figueredo et al., 2011)
	1,10-phenanthroline assay (Fe^{2+} concentration)		25, 50 and 100 μM	Decrease in Fe^{2+} levels	Stimulation of Fe^{2+} to Fe^{3+} oxidation	
	Oxygen consumption assay	Guttiferone A	25 μM	Increase on rate of oxygen consumption 115.3 ± 5.16 nmol O_2/ml per min	Guttiferone A oxidizes Fe^{2+} to its ferric form requiring O_2 as an electron acceptor	(Figueredo et al., 2011)
		Guttiferone A	50 μM	Increase on rate of oxygen consumption 184.0 ± 3.94 nmol O_2/ml per min		
		Guttiferone A	100 μM	Increase on rate of oxygen consumption 203.8 ± 4.48 nmol O_2/ml per min		
		Guttiferone A	200 μM	Increase on rate of oxygen consumption 234.68 ± 5.25 nmol O_2/ml per min		
In vitro – (MDA assay)	*In vitro - rat's brain homogenate*	Guttiferone A	0.01, 0.1, 10 and 100 μM	Inhibition of iron-induced lipid peroxidation (MDA - malondialdehyde formation)	By decreasing the amount of Fe2+ which is involved in the formation of •OH radicals, oxidative stress is avoided	(Figueredo et al., 2011)
	Comet (genotoxicity)	Guttiferone A	15, 30 and 60 mg/kg	Genotoxicity evidenced by increase in DNA		(Terrazas et al., 2013)

In vivo - (male *Swiss* mice)				damage to mice leukocytes, liver, bone marrow, brain and testicle cells	Nuclear fragmentation induced by oxygen reactive species production	
	Micronucleus test (mutagenicity)			Mutagenicity evidenced by aneugenic effects on cells under guttiferone A treatment		
In vitro – (enzimatic inhibition)	Cathepsin B inhibition assay	Guttiferone A	0.51g	IC_{50} = 2.1 ± 0.2 µM	High chemical compatibility	(Kolodziejczyk et al., 2009)
	Papain inhibition assay	Guttiferone A		IC_{50} = 1.9 ± 0.1 µM		(Kolodziejczyk et al., 2009)
	Trypsin inhibition assay	Guttiferone A		IC_{50} = 9.4 ± 0.3 µM	Moderately high inhibitory action due to low chemical compatibility	(Kolodziejczyk et al., 2009)
In vivo - (Male *Swiss* mice)	Ethanol/HCl-induced ulcer	Guttiferone A	30 mg/kg	73.6 ± 17.9 % of ulcer formation inhibition	Decrease of gastric secretion	(Niero et al., 2012)

Differences in the molecular structure of guttiferones have a strong influence on their biological activity, as seen in the case of guttiferone Q, which differs from the other guttiferones by the absence of the hydroxyl groups on the phenolic ring (Figure 2 and Table 2). This slight structural difference had the effect of drastically reducing the antioxidant activity of guttiferone Q when compared with other guttiferones and standards such as ascorbic acid. Further research should confirm that said molecular groups are the main responsible for this activity or not (Trinh et al., 2014). Guttiferone A also has chemical particularities that enhances its lipophilicity, making it easier to trespass biological membranes and thus exert its antioxidant activity (Figueredo et al., 2011) (Pardo-Andreu et al., 2011).

Although studies have addressed the antioxidant activity of some of the guttiferones, little was discovered about the mechanism of action by which they exert such activity, an issue to consider in further research.

4.2 Anti-inflammatory activity

Inflammation, a physiological response to injuries or infection, is frequently associated with a number of diseases. Thus, some treatment strategies focus on attenuating the four essential components of inflammation: inducers, which are pathogens or an injury that starts inflammation; sensors, cells from the immune system (e.g., mast cells and macrophages) that senses inducer's presence; mediators, molecules such as cytokines that inhibit or stimulate cells actions towards inflammation; and target tissues (Okin & Medzhitov, 2012).

Macrophages are immune system cells of great importance that secrete pro-inflammatory cytokines promoting host defense. However, they can also prolong inflammation in some diseases, such as tuberculosis and chronic wound healing (Kundu et al., 2021) (Wang, Han, Owens, Siddiqui & Li 2006). Compounds that can mitigate these cells' actions as inflammation promoters may improve therapies for these diseases, and guttiferone E, K and M were noted as anti-inflammatory molecules, as shown in Table 3 and below.

The study of Zhang et al. (2020) investigated the potential of Guttiferone K in modulating the immune system by acting in macrophages infected with *Mycobacterium tuberculosis.* As result, guttiferone K reduced the levels of IL-1β, TNF-α and IL-6 - inflammatory mediators produced in high amounts by *M. tuberculosis*-infected macrophages - which could prolong inflammation and further lung tissue damage seen in tuberculosis (Surh et al., 2001; Zhang et al., 2020).

M. tuberculosis-infected macrophages, besides producing cytokines, have a complex of intracellular proteins called the inflammasome. This complex is responsible for the maturation of other pro-inflammatory cytokines namely IL-1β and IL-18, which stimulate the inflammatory process (Qin et al., 2021). Therefore, inhibiting the formation/activation of this protein complex (inflammasome) is one strategy to avoid inflammation (Xu et al., 2020). It is known that guttiferone K treatment leads to inhibition of IL-1β actions, and thus Zhang et al. (2020) observed if it is related to inflammasome inactivation. The results showed that, with the addition of guttiferone K into the cell culture, inflammasome proteins and IL-1β expression diminished. Therefore, they concluded that guttiferone K inhibits inflammasome activation and the subsequent events that stimulate inflammation (Zhang et al., 2020).

It was also evaluated the inhibitory activity of Guttiferone K on activation of NF-κB by TLR/IRAK-1 signaling pathway. Toll Like Receptors (TLRs) are found in the cellular membrane of macrophages, T cells, and other types of cells, and serves as places to interact with pathogens structures, named as pathogen-associated molecular pattern molecules (PAMPs), such as peptidoglycan, bacterial DNA and lipopolysaccharide (LPS) (Liu & Cai, 2018). When those structures are recognized by a TLR, several reactions occur and signaling pathways such as TLR/IRAK-1 are activated. The active TLR/IRAK-1 pathway stimulates NF-κB that is responsible for the production of inflammatory mediators (Das et al., 2016). When Guttiferone K was added to the cell culture, it was observed that phosphorylation levels on cells were low along with the activation of IRAK-1 proteins and the subsequent reactions. Thus, the anti-inflammatory activity of Guttiferone K is related to its ability to inhibit the TLR/IRAK-1 pathway (Zhang et al., 2020).

MAPK signaling pathway is also involved in inflammatory processes, given the fact that it can be activated by TLRs. It involves molecules such as p38, JNK and ERK that are highly phosphorylated in primary and RAW264.7 macrophages that were infected by M. tuberculosis. When administered Guttiferone K on both cell cultures, no significant effect on MAPK signaling pathway was observed, which would be evidenced by the decrease in the phosphorylation of p38, JNK and ERK. Thereby, it was concluded that the anti-inflammatory effects of Guttiferone K occur through modulation of TLR/IRAK-1 signaling pathway, which ends on the inhibition of NF-κB, with no influence on MAPK pathway (Zhang et al., 2020).

Autophagy, a cellular process in which cytoplasmic constituents are transported to lysosomes for degradation, with the aim of recycling cellular components, can also inhibit inflammation. In the autophagic process, molecules responsible for activating the inflammasome are degraded as well (Cao et al., 2019). Other studies showed that guttiferone K induces autophagy in tumoral cells and cellular death by apoptosis (Zhang et al., 2021). Hence, Zhang et al. (2020) showed that guttiferone K stimulates autophagy in macrophages infected with *M. tuberculosis*, which could explain why inflammasome proteins were downregulated. The akt/mTOR signaling pathway, along with MAPK and IRAK-1, is a downstream pathway of the activation of TLR, and when inhibited it is known to stimulate autophagy (Wen, Zhang, Wang & Li, 2020). Guttiferone K treatment of the primary and RAW264.7 led to decrease in phosphorylation and therefore inactivation of Akt and mTOR in

both cell cultures. Thus, Guttiferone K inhibits TLR/Akt/mTOR signaling pathway, activating autophagy and as a result inhibiting inflammation (Zhang et al., 2020).

Guttiferone E is another PPAP with anti-inflammatory action, as described by Dzoyem et al. (2015). They applied the guttiferone to an LPS (bacterial lipopolysaccharide)-stimulated RAW 264.7 macrophage culture, the elevated inflammatory state of which was evidenced by the high nitric oxide production. Excessive levels of nitric oxide are known to result in the cellular damage found in Alzheimer's disease, hypotension, osteoarthritis, atherosclerosis, and chronic inflammation of adipose tissues, for example (Ghanim et al., 2021). Guttiferone E was toxic at concentrations greater than 25 μg/mL, in agreement with data from other groups (Dzoyem et al., 2015). However, it inhibited the production of nitric oxide by the cells, indicating that the guttiferone is a potent anti-inflammatory molecule (see more information in Table 3). Nonetheless, more studies are needed to determine the balance between cytotoxicity and anti-inflammatory properties (Dzoyem et al., 2015).

4.3 Antitumor activity

Guttiferones are also known to have antitumor effects against some types of cancer, the mechanisms of action having been elucidated by *in vitro* and *in vivo* studies, summarized in Table 4. The PPAPs, especially types A, F, and K, that seem to decrease invasiveness of cancer cells as well as promoting cell death.

A group of proteins named profilins has been currently associated with cell proliferation, migration and invasiveness, being profilin 1 (PFN1) linked to some types of human cancer and hepatocellular is one of them. In other experiments, it was observed that the overexpression of profilin 1 could inhibit migration and therefore metastasis (Wang, Shi, Zhang, L., Zhang, H. & Zhang, Y. 2019). Shen et al. (2016) made an insight on that matter.

Matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry (MS) analysis along with western blot and PCR analysis was made to get a protein profile of the cell cultures treated with Guttiferone K and the ones that received only vehicle. Profilin 1 was one of the 30% of the up-regulated proteins in the guttiferone K group. Because of that, the effect of high levels of PFN1 on cell motility was evaluated, and the results showed a decrease in invasion ability of HepG2, Li-7 and PLC/PRF/5 cells. By further analysis, Guttiferone K showed to be a PFN1 levels increasing factor, using this pathway to decrease cell motility and metastasis (Shen et al., 2016).

In vivo experiments were also made confirming that up-regulation of PFN1 is related to metastasis suppression. By immunohistochemistry analysis, they evaluated PFN1 expression on 86 advanced human hepatocellular cancer samples and recognized a pattern of low levels of the protein in those cancer tissues in comparison to non-cancer tissues. The conclusion of this study was that Guttiferone K inhibits hepatocellular carcinoma metastasis by restoring the aberrantly reduced PFN1 levels on tumor cells, and that the protein could be a promising biomarker for the disease (Shen et al., 2016).

Table 4. Antitumor effect and mechanisms of guttiferones in *in vitro* and *in vivo* assays.

Model	Assay	Substance	Dose/Concentration	Effect	Mechanisms	Reference
Antitumor						
In vitro – (HeLa-C3 cells)	Apoptotic assay	Guttiferone E	25, 50 and 100 μM	Apoptosis induction	Caspase-3 activation	(Liu et al., 2010)
		Guttiferone F	25 and 100 μM	Apoptosis induction	Caspase-3 activation	
In vitro – (HeLa and Capan-2 cells)	Apoptotic assay	Guttiferone K	5 μM	Apoptosis induction	Increase of Sub-G1 cells population in nutrient-deprived conditions by caspase-3 and PARP activation	(Wu et al., 2015)
In vitro – (PC-3 and LNCaP cells)	Western blotting assay	Guttiferone F	10 and 20 μM	Apoptosis induction	Increase in sub-G1 fraction cells, Activation of caspase-9, −7 and −3. Production of cleaved PARP and Bcl-2 degradation. Up-regulation of phosphorylated JNK proteins and down-regulation of phosphorylated ERK	(Li et al., 2015)
In vivo – (BALB/c nude mice)	Tumor size, volume and weight measurement (PC3 cells xenograft tumor model)	Guttiferone F	20 mg/Kg	Decreased tumor growth when combined with caloric restriction (compared to the control group)	Apoptosis induction and cell proliferation inhibition	(Li et al., 2015)
In vitro – (HepG2 cells)	Annexin-V/propidium iodide double-staining	Guttiferone A	25 μM	Cell viability decrease (around 50% cell death)	Mitochondrial energetic impairment	(Pardo-Andreu et al., 2011)
In vitro – (CCRF-CEM cells)	Apoptotic assay	Guttiferone E	6.86 μM	17.42-fold increase on caspase 3/7 activity; 4.7-fold increase on caspase 8 activity;	Caspase-3,7,8 and 9 activations	(Kuete et al., 2013)

				3.8-fold increase on caspase 9 activity		
In vitro – (HCT-116 and HT-29 cells)	MTT assay (cell viability)	Guttiferone A	3.125, 6.5, 12.5, 25, 50 and 100 µg/mL	IC_{50} = 5 µM	High cytotoxicity against HCT-116 and HT-29 cells	(Yang et al., 2010)
In vitro – (SW-480 cells)	MTT assay (cell viability)	Guttiferone A	3.125, 6.5, 12.5, 25, 50 and 100 µg/mL	IC_{50} = 21 ± 4.0 µM	High cytotoxicity against SW-480 cells	(Yang et al., 2010)
In vitro – (HCT-116, HT-29 and SW-480 cells)	MTT assay (cell viability)	Guttiferone K	3.125, 6.5, 12.5, 25, 50 and 100 µg/mL	IC_{50} = 10 µM / 25 µM/ 23 ± 2.6 µM	High cytotoxicity against HCT-116, HT-29 and SW-480 cells	(Yang et al., 2010)
In vitro – (SW-480 cells)	MTT assay (cell viability)	Guttiferone E	3.125, 6.5, 12.5, 25, 50 and 100 µg/mL	IC_{50} = 7.5 µM	High cytotoxicity against SW-480 cells	(Yang et al., 2010)
In vitro – (SW-480 cells)	MTT assay (cell viability)	Guttiferone H and E	8, 16 and 25 µM	IC_{50} = 12.4 µM / 7.5 µM	High cytotoxicity against SW-480 cells	(Baggett et al., 2005)
In vitro – (LNCaP, PC-3, HepG2, HeLa and CNE cells)	MTT assay (cell viability)	Guttiferone F	Not reported	IC_{50} = 5.17 ± 0.20 µM / 12.64 ± 3.01 µM/ 32.93 ± 1.56 µM / 13.13 ± 1.32 µM and 17.97 ± 1.30 µM	High cytotoxicity against LNCaP, PC-3, HepG2, HeLa and CNE cells	(Li et al., 2015)
In vitro – (SW620, BT424, HepG2, KATO-III and CHAGO cells)	MTT assay (cell viability)	Guttiferone K	Not reported	IC_{50} = 0.0017 / 9.91 / 0.13 / 0.13 and 0.10 µM	High cytotoxicity against SW620, BT424, HepG2, KATO-III and CHAGO cells	(Mungmee et al., 2015)
In vitro – (HeLa, HepG2 and AGS cells)	MTT assay (cell viability)	Guttiferone F	5, 10, 20 and 40 µM	IC_{50} = 35.7 / IC_{50} = 35.7 and IC_{50} > 50 µM	High cytotoxicity against HeLa, HepG2 and AGS cells	(Tang et al, 2015)
In vitro – (HT-29 cells)	MTT assay (cell viability)	Guttiferone A	15.8 µM	IC_{50} = 9.5 µg/mL	Activation of the endoplasmic reticulum stress response and inhibition of the mammalian	(Einbond et al, 2013)
		Guttiferone E	7.8 µM	IC_{50} = 4.7 µg/mL		

					target of rapamycin (mTOR) cell survival pathway	
In vitro – (A2780 cells)	Neutral Red (cell viability)	Guttiferone A	Not reported	IC_{50} = 6.8 µg/mL	High cytotoxicity against A2780 cells	(Williams et al, 2013)
		Guttiferone G		IC_{50} = 8.0 µg/mL		
In vitro – (CCRF-CEM cells)	Resazurin reduction assay (cell viability)	Guttiferone E	Not reported	IC_{50} = 6.86 µM	High cytotoxicity against CCRF-CEM cells	(Kuete et al., 2013)
In vitro – (HL60 cells)				IC_{50} = 11.69 µM	High cytotoxicity against HL60 cells	
In vitro – (MDA-MB-231 pcDNA, HCT116 (p53+/+ and U87MG cells)	Resazurin reduction assay (cell viability)	Guttiferone E	Not reported	IC_{50} = 11.69 µM / 12.74 µM and 7.87 µM	High cytotoxicity against MDA-MB-231 pcDNA, HCT116 (p53+/+ and U87MG cells	(Kuete et al., 2013)
In vitro – (HepG2, CEM/ADR5000 and HL60AR cells)	Resazurin reduction assay (cell viability)	Guttiferone E	Not reported	IC_{50} = 11.13 µM/ 13.57 µM and 11.69 µM	High cytotoxicity against HepG2, CEM/ADR5000 and HL60AR cells	(Kuete et al., 2013)
In vitro - MDA-MB-231 BCRP, HCT116 (p53-/-), U87MGΔEGFR and AML12 cells	Resazurin reduction assay (cell viability)	Guttiferone E	Not reported	IC_{50} = 13.92 µM / 7.87 µM / 3.39 µM and IC_{50} > 66.45 µM	High cytotoxicity against MDA-MB-231 BCRP, HCT116 (p53-/-), U87MGΔEGFR and U87MG, AML12 cells	(Kuete et al., 2013)

In vitro – (MCF-7, HeLa, NCI-H460 cells)	SRB assay (cell viability)	Guttiferone Q	Not reported	IC_{50} = 2.74 µM / IC_{50} = 3.03 µM and IC_{50} = 4.04 µM	High cytotoxicity against MCF-7, HeLa, NCI-H460 cells	(Nguyen et al., 2011)
In vitro – (MeWo cells)	LDH assay (Cytotoxic activity)	Guttiferone A	25 µM	80% of cell death	Decrease of the melanin content	(Mulholland et al., 2013)
In vitro – (HEL, K562 and Hela cells)	MTT assay (cell viability)	Guttiferone E and Xanthocymol (GX)	1 µM, 2.5 µM, 5 µM, 10 µM, and 20 µM	IC_{50} = 18.70 ± 0.07 µM / 18.12 ± 1.05 µM and 9.06 ± 0.31 µM	High cytotoxicity against HEL, K562 and Hela cells	(Lin et al., 2019)
In vitro – (MCF-7 and A549 cells)	MTT assay (cell viability)	Guttiferone E and Xanthocymol (GX)	1 µM, 2.5 µM, 5 µM, 10 µM, and 20 µM	IC_{50} = 7.77 ± 0.07 µM and 10.13 ± 0.86 µM	High cytotoxicity against MCF-7 and A549 cells	(Lin et al., 2019)
In vitro – (LNCaP and PC-3 cells)	Fluo-4 Calcium Assay (cytosolic Ca^{2+} concentration)	Guttiferone F	10 µM	Elevation on cytosolic Ca^{2+} concentration	Activation of MAPK signaling pathways	(Li et al., 2015)
In vitro – (LNCaP and PC-3 cells)	Cell death and DNA morphology	Guttiferone F	20 µM	Chromatin condensation and DNA fragmentation	Cell death induction	(Li et al., 2015)
In vitro – (Hepg2 cells)	Mitochondrial membrane potential	Guttiferone A	1, 5, 10 and 25 µM	Mitochondrial energetic impairment	Extensive mitochondrial membrane potential dissipation	(Pardo-Andreu et al., 2011)
In vitro – (Hepg2 cells)	DCFH-DA assay (Cellular ROS)	Guttiferone A	1, 5, 10 and 25 µM	Mitochondrial energetic impairment/oxidative	ROS levels increase	(Pardo-Andreu et al., 2011)
In vitro – (Liver mitochondria isolated from Wistar rats)	Mitochondrial ATP assay	Guttiferone A	5 µM	45% of ATP levels decrease	Energetic impairment caused by the dissipation of the mitochondrial membrane potential	(Pardo-Andreu et al., 2011)

In vitro – (Liver mitochondria isolated from Wistar rats)	Mitochondrial ATP assay Amplex Red assay (H_2O_2 release)	Guttiferone A	25 μM	65% of ATP levels decrease	Energetic impairment caused by the dissipation of the mitochondrial membrane potential Mitochondrial energetic impairment/oxidative stress / Increased H_2O_2 levels in isolated rat-liver mitochondria	(Pardo-Andreu et al., 2011)
			5, 10 and 20 μM	7.22 ± 0. 14 nmol/ml / 9.11 ± 0.14 nmol/ml / 10.9 ± 0.16 nmol/ml		
In vitro – (Liver mitochondria isolated from Wistar rats)	Mitochondrial membrane fluidity by fluorescence spectrophotometry	Guttiferone A	5, 10 and 25 μM	Decrease in fluorescence anisotropy (r)	Mitochondrial energetic impairment / Increased mitochondrial membrane fluidity	(Pardo-Andreu et al., 2011)
In vitro – (CCRF-CEM cells)	Mitochondrial membrane potential assay	Guttiferone E	Not reported	98.3% of mitochondrial membrane potential alteration	Activation of caspases 3, 7, 8 e 9	(Kuete et al., 2013)
In vitro – (MCF-7 cells)	Mitochondrial membrane potential assay	Guttiferone A	0, 7.5, 15 and 30 μM	IC_{50} = 15μM	Increasement of intracellular ROS levels and reduction of the mitochondrial membrane potential (MMP)	(Wu & Li, 2017)
In vitro – (NCI-H460 cells)	SRB assay (cell viability)	Guttiferone I	100 μg/mL	91.9% of growth inhibition	Cell growth inhibition	(Nguyen et al., 2011)
In vitro – (HeLa cells)	SRB assay (cell viability)	Guttiferone I	50 μg/mL	82.7% of growth inhibition	Cell growth inhibition	(Nguyen et al., 2011)
In vitro – (MCF-7 cells)	SRB assay (cell viability)	Guttiferone I	50 μg/mL	80% of growth inhibition	Cell growth inhibition	(Nguyen et al., 2011)
In vitro – (hepatocellular carcinoma cells)	Migration and invasion assay	Guttiferone K	1, 2.5, 5, 10 and 20 μM	Reduced motility and invasion capacities	Restoration of reduced PFN1 protein expression in cancer cells	(Shen et al., 2016)

In vivo – (BALB/c nude mice)	Migration and invasion assay	Guttiferone K	3 and 10 mg/kg	Reduction on the number of metastasized nodules in the lungs	Restoration of reduced PFN1 protein expression in cancer cells	(Shen et al., 2016)
In vitro – (HepG2, Li-7 and PLC/PRF/5 cells)	Western blotting assay	Guttiferone K	20 μM	Reduced motility and invasion capacities	Up-regulation of PFN1 expression in HepG2	(Shen et al., 2016)
In vitro – (HepG2 cells)	Migration and invasion assay	Guttiferone K	1, 2.5, 5, 10 and 20 μM	Reduced motility and invasion capacities	Decrease in actin filaments (F-actin)	(Shen et al., 2016)
In vitro – (HeLa, Capan-2 and CNE cells)	GFP-LC3 translocation assay (Autophagy)	Guttiferone K	20 μM	Autophagy induction	Increase on autophagosomes production and enhanced p62 degradation	(Wu et al., 2015)
In vitro – (HeLa cells)	DCFH-DA assay (ROS detection)	Guttiferone K	5 μM	Autophagy induction	Enhanced ROS production JNK activation under nutrient starvation	(Wu et al., 2015)
In vitro – (HeLa, Capan-2 and CNE cells)	Western blotting assay	Guttiferone K	5 μM	Autophagy induction	Decrease on Akt and mTOR phosphorylation levels in nutrient starvation conditions	(Wu et al., 2015)
In vitro – (LNCaP cells)	Western blotting assay	Guttiferone F	10 μM	Growth inhibitory effect against prostate cancer cells under serum starvation	Significant reduction in androgen receptors expression	(Li et al., 2015)

In addition to limiting cell mobility, some antitumor drugs use oxidative stress as a strategy to eliminate cancer cells by interacting with one of the essential organelles of reactive oxygen species (ROS) production: the mitochondria. This interaction depends on the ability of the drug in crossing the mitochondrial membrane, and it is required for that molecule to be lipophilic enough (Zinovkin and Zamyatnin, 2019).

Guttiferone A, as noted by Pardo-Andreu's (2011) group, has the necessary features to transit the mitochondrial membrane. *In vitro* experiments with HepG2 cells showed that guttiferone A affects cell viability, mitochondrial membrane potential, ATP, and ROS levels. These events are preceded by the dissipation of the mitochondrial membrane potential. Guttiferone A at 25 μM caused 50% of cell death, similar to the positive control, the uncoupler CCCP (Carbonyl cyanide m-chlorophenylhydrazone), which reduces mitochondrial membrane potential. Further analysis showed that ROS accumulation (oxidative stress), mitochondrial membrane permeabilization, ATP depletion and final cellular energetic impairment were the mechanisms that caused cell death, thus confirming that guttiferone A has antitumoral capacities (Pardo-Andreu et al., 2011). Similar results were found by Wu and Li (2017) in a human breast cancer cell culture (MCF-7), besides highlighting that guttiferone A induces apoptosis through stimulating Bax expression (pro-apoptotic protein) and inhibiting Bcl-2 expression (antiapoptotic protein) (Table 4).

Oxidative stress, apart from being a cellular death trigger, activates survival pathways such as MAPK (mitogen-activated kinase) and nuclear factors like NF-kB and AP-1. The latter are responsible for drug resistance mechanisms activation in tumoral cells. Considering the sound antitumor effects of guttiferone K and its ability to increase oxidative stress in tumoral cells, Boonyong and contributors (2017) tested and concluded that the compound stimulates drug resistance similarly to doxorubicin hydrochloride, an everyday use drug for human colon adenocarcinoma therapy.

Besides stimulating oxidative stress, one way of turning tumoral cells more susceptible to death or apoptosis is by depleting the cell's nutrients, making them undergo starvation apoptosis. Li et al. (2015) tried guttiferone F as an antitumoral substance in a nutrient-depleted tumoral cells culture, having as a result in the inhibition of the proliferation of all tested cell lines (see Table 4 for more information).

Some cancer cell lines are not affected by the guttiferones. An example is a study by Cao et al. (2007) using guttiferones L and K against the A2780 human ovarian cancer cell line. On the other hand, it is possible to mix two different guttiferone to have stronger actions as they work in synergism, as Yang et al. (2010) showed by testing guttiferone A and K against SW-480 (colon cancer) cells and having significant antitumor results. The synergy occurs not only between guttiferones: Einbond et al. (2013) presented an association of guttiferone E and sulindac sulfide, a non-steroidal anti-inflammatory drug (NSAID) that, when applied to an

HT29 human colon cancer cell culture presented good cytotoxicity (Table 4). The same synergic effect was found in the mixture of guttiferone E and celecoxib, another NSAID, opening a field of future possibilities in using PPAPs of natural origin in treating cancer (Einbond et al., 2013).

4.4 Antiparasitic Activity

Neglected tropical diseases (NTDs) are a group of diseases that significantly affect the poor population of underdeveloped/developing countries. Schistosomiasis, malaria leishmaniasis, and Chagas disease are some listed NTDs that still have few treatment advances (Schmidt et al., 2012). For that matter, new substances with antiparasitic activity are in need, and the guttiferones A and F showed exciting results, as shown in Table 3 and below.

The current drug for schistosomiasis treatment, praziquantel, is ineffective against some of the parasite forms and does not prevent reinfections. Besides, drug-resistant strains were reported, bringing one more concern to the health authorities. Barros et al. (2015) showed that guttiferone A has activity against *Schistosoma mansoni*, although the mechanism is still not well understood. Pereira et al. (2010) confirmed that guttiferone A is not toxic to host macrophages, another reason that favors the application of the guttiferone in treating schistosomiasis.

As mentioned above, few improvements have been obtained recently in treatment strategies for parasite diseases, such as malaria. The latest achievement in terms of malaria treatment is the development of a vaccine, as shown in the work of Datoo et al. (2022). Chloroquine is still the typical treatment for malaria even with the high toxicity that the drug presents to the patient (Zhou et al., 2020). Guttiferone A, tested by Ngouela et al. (2005) against *P. falciparum*, the protozoan that causes malaria, showed to be even better than chloroquine, needing further research to understand mechanisms and cytotoxic effects better.

Pereira et al. (2010) and Lenta et al. (2007) observed the same pattern, this time for treating leishmaniasis: guttiferone A presented better leishmanicidal activity than the positive controls, amphotericin B and miltefosine. Similar results were gathered by Lenta et al. (2007) using guttiferone F against *Leishmania donovani* (Table 3). Therefore, guttiferones A and F seem promising in treating important NTDs, serving as alternative treatments with fewer side effects than the current drugs.

4.5 Antimicrobial activity

Infectious diseases remain an obstacle to public health despite significant progress in human medicine. Their control remains an enormous challenge, given the emergence of multidrug-resistant microorganisms (Saga and Yamaguchi, 2009). *S. aureus* is one example of bacteria with drug resistance mechanisms that result in around 11,000 to 18,000 deaths per year only in the United States of America (Hiramatsu K., 2001) (Liu et al., 2021).

Guttiferone A inhibited the growth of the gram-positive bacteria *S. aureus* and *B. cereus* in the experiment by Naldoni et al. (2009). Against gram-negative bacteria (*Escherichia coli*), however, the guttiferone had no effects, as shown by Naldoni et al. (2009) and Monzote et al. (2011) (see Table 3 for further information). This selectiveness is because gram-positive bacteria have a lipophilic membrane that is easily crossed by guttiferone A, one of the most lipophilic guttiferones (Echeverría, Opazo, Mendoza, Urzúa & Wilkens, 2017).

Antibiotics against gram-positive bacteria - such as gentamicin (GEN) and ampicillin (AMP) - also have lipophilic features to access bacterial cells (Echeverría, Opazo, Mendoza, Urzúa & Wilkens, 2017). Both drugs are in everyday use in treating bovine mastitis, a disease caused by *Streptococcus spp.* that leads to high financial losses in the dairy industry (De Vliegher et al., 2012). Therefore, Maia et al. (2018) tested the potential of guttiferone A against *Streptococcus spp.* when administered with GEN and AMP, seeking synergism between the substances. Both associations (GEN and Guttiferone A; AMP and Guttiferone A) had satisfactory synergistic activity, suggesting its usefulness in mastitis treatment.

Against gram-negative bacteria, the recently described guttiferone BL might be helpful since it showed antimicrobial activity against *E. coli*, *Klebsiella pneumoniae*, and *Enterobacter aerogenes*, responsible for many opportunistic infections in hospitals. Even though this activity was low compared to standards, further research on the molecular structure of the guttiferone and even synergist studies should fill this gap (Nganou et al., 2018).

Fungi from the Candida genus are frequently studied for their clinical importance as biofilm-producing organisms with increasing drug resistance mechanisms, demanding new treatments to overcome the situation. *Candida albicans* is the main cause of bloodstream infection, leading to morbidity and death. On the other hand, through the years, non-albicans species have been responsible for at least 50% of this type of infection (Arendrup & Patterson, 2017). Therefore, Naldoni et al. (2009) and Monzote et al. (2011) tested guttiferone A against

C. albicans, having no effects as a result; while Dias et al. (2012) and De Carvalho et al. (2018) tested against non-albicans species, this time an antifungal activity was observed (Table 3). Moreover, for *Candida krusei*, there was an excellent synergistic antifungal effect between guttiferone A and fluconazole, a drug of everyday use in fungal diseases. Further experiments should help to understand the mechanisms by which guttiferone A exerts its effects against microorganisms and synergistic events that can be useful in clinical practice.

4.6 Immunomodulatory effect on MHC and VCAM related molecules

Tumor cells and virus-infected cells can escape the immune response through modulation of major histocompatibility complexes (MHCs), a group of proteins responsible for presenting peptide antigens to T cells. Because of that, some drugs used for cancer treatment use the strategy of decreasing MHCs expression or changing the structure of related receptors in order to avoid immunosuppression (Xing and Ferrari de Andrade, 2020).

There are two types of MHC - class I and class II. Class II MHC is in the vast majority of cell types, and presents antigens for CD4 T cells, also known as T helper cells. Class I MHC, on the other hand, presents antigens for CD8 T cells that will give rise to cytotoxic T lymphocytes and Natural Killers (NK) cells whose function is to eradicate tumor cells and infected cells, respectively. In order to increase lymphocyte activation during the immune response or in inflammatory responses, the body produces molecules such as Interferon gamma (IFNγ) and TNF-α to further stimulate the expression of MHCs. When present, IFNγ transduces signals via the JAK-1/STAT-1 pathway (López-García and Castro-Manrreza, 2021) (Gough, Levy, Johnstone, & Clarke, 2008) (Scott et al., 2018).

In the experiment made by Coste et al. (2020), guttiferone F, guttiferone J, xanthocymol, and xanthocymol in a mixture with guttiferone F were isolated from *Garcinia bancana* barks. When a human primary vascular endothelial cell culture (HUVEC) subjected to a IFN-γ and TNF-α induced inflammatory state received guttiferone F, all types of MHCs had their stimulatory activity on cytokines production inhibited. This inhibitory effect was quantitatively similar to guttiferone J. Isolated guttiferone F also inhibited cytokine production to a greater extent than isolated xanthocymol, which was expected because of the structural similarities seen by molecular docking (Coste et al., 2020).

Inflammation is an immune system strategy to eliminate pathogens. During inflammation, endothelial cells are activated. In that state, they activate natural killer (NK)

cells, CD4 and CD8 T cells by expressing membrane surface molecules such as vascular cell adhesion molecules (VCAM-1) and major histocompatibility complexes (MHCs) (Habas and Shang, 2018). Endothelial cell activation is reversible. However, in some situations, this activated state remains, leading to endothelial dysfunction as seen in cardiovascular diseases and the rejection process of transplanted organs, demanding drugs capable of interrupting the activated state of these cells (Yang et al., 2016).

In the study by Rouger et al. (2016), VCAM-1 production by endothelial cells were evaluated after the addition of gutiferone J to the HUVEC cell culture, previously subjected to an inflammatory state. The PPAP showed an inhibitory effect over VCAM-1 expression in a range of 20% to 60%. Consequently, endothelial cells became less active, and few immune cells were activated. MHCs expression also diminished, a result obtained by Coste et al. (2020) likewise using guttiferones J and F. Finally, Rouger et al. (2016) concluded that guttiferone J has immunosuppressive and anti-inflammatory properties that may decrease endothelial cell surface markers that participate in endothelial dysfunction and the rejection of transplanted organs. Coste et al. (2020) include guttiferone F in these results, more details are available in Table 3.

4.7 Other pharmacological activities

Besides the said effects, guttiferones may act in a variety of situations as therapeutic agents. Guttiferone A remains under investigation for its use in the treatment of HIV, iron intoxication, and gastric ulcers described below.

Guttiferone A might be an anti-HIV agent, thanks to its ability to inactivate a group of enzymes called proteases. hese are enzymes that hydrolyze peptides and have an important role in protein metabolism (Agbowuro, Huston, Gamble & Tyndall, 2018). Human immunodeficiency virus (HIV) also has proteases that are essential for the virus maturation and activation, and therefore, the use of protease inhibitors is one strategy to control HIV replication and disease aggravation (Laco, 2017). Martins et al. (2009) isolated guttiferone A from fruits and seeds of *Garcinia brasiliensis* and tested it against the following proteases: papain, trypsin, cathepsin G and cathepsin B.

Cathepsin B, a cysteine protease, has a molecular structure similar to papain, however, it is not functional in neutral and alkaline pH environments that are common in healthy cells. In cancer cells, though, cathepsin B is found in large amounts and helps with rupture of tissues

and tumor spreading. HIV-infected cells show the same pattern of cancer cells when concerning cathepsin concentrations (Cantres-Rosario et al., 2019). Cathepsin G is a serine protease found in the extracellular matrix and inside immune system cells and also has a role in HIV infection (Burster, Knippschild, Molnár & Zhanapiya et al., 2020).

By *in vitro* tests with guttiferone A, Martins et al. (2009) showed that the PPAP inhibits the proteases papain, trypsin, cathepsin G, and cathepsin B, being most selective to cathepsin G with IC_{50}, similar to the control group that received a classic cathepsin G inhibitor, chymostatin (Table 3). Papain, trypsin and cathepsin B were also inhibited, however in lower levels, probably because of the chemical compatibility of the guttiferone, a lipophilic compound, and the said enzymes that belong to the trypsin-like hydrolases group. Through inhibition tests, Martins et al. (2009) determined that guttiferone A exerts its effects by non-competitive inhibition, with the formation of an irreversible bond between the compound and the enzyme. In this way, guttiferone A may produce anti-HIV effects by inhibiting enzymes responsible for virus maturation and proliferation processes.

Another class of enzymes, the histone acetyltransferase enzyme (HATs), are responsible for modifications on nuclear proteins that influence DNA repair. Because of that, they are targeted for different cancer types therapies (Barneda-Zahonero and Parra, 2012). For that matter, Dal Piaz et al. (2010) showed that guttiferone A inhibited these enzyme activities in a similar way as some HAT inhibitor drugs - such as romidepsin - in an i*n vitro* experiment, besides presenting antiproliferative capacities as well, measured by cytotoxicity tests (Table 3).

The same guttiferone was studied for its antiulcerogenic activities, such as the experiment made by Niero et al. (2012). Using an HCl/Ethanol gastric ulcer-induced model on mice, they found guttiferone A to diminish wounded areas in a range similar to that obtained with the control substance, omeprazole, a proton-pump inhibitor commonly used as an antiulcerogenic drug (Table 3).

Since guttiferone A acts as an antioxidant compound with likely chelating activities, Figueredo et al. (2011) tested it *in vitro* against brain cells under iron excess conditions. Iron is a necessary metal to the human body, as can be seen in oxygen transport by hemoglobin, for example. However, high levels of iron may induce damages for cells, especially because of its ability to convert into its reduced Ferrous Fe2+ and oxidized ferric Fe3+ forms that cooperate

to reactive oxygen species production, which can help with the development of some neurodegenerative diseases such as Alzheimer and Parkinson (Carocci, Catalano, Sinicropi, & Genchi, 2018).

Using an iron chelator agent along with an antioxidant agent is a currently pursued strategy to avoid neuronal diseases (García-Beltrán et al., 2017). Since Guttiferone A acts as a antioxidant compound, and there are few studies about its chelating activities, Figueredo et al. (2011) tested it on PC12 cells, which are pheochromocytoma cells from rats and primary culture of rat cortical neurons (PCRCN) subjected to different concentrations of Guttiferone A.

Firstly, cell viability tests were performed and at a concentration of 50 μM, the guttiferone was not toxic to any of the cell lines. The viability of iron toxicity induced cells was increased with the addition of 0.01 μM - for PC12 cells - and 0.05 μM for PCRCN of Guttiferone A. The final results showed that guttiferone A can protect brain cells from iron induced death by its ability to interact with iron and prevent it from producing reactive species. The fact that Guttiferone A has a high lipophilicity may explain its efficiency on interacting and protecting cells. The chelant potential of guttiferone A could be explained by the catechol group in its structure, a common feature in chelant agents. Guttiferone A could possibly transpass the blood brain barrier for its lipophilic quality, however, as an antioxidant agent, to get to the brain and perform its therapeutic action, it should compete with other molecules on its way. It would be necessary to increase the amount of Guttiferone administered to at least some millimoles, a step that still needs to be studied (Figueredo et al., 2011).

Besides damaging cells by creating reactive oxygen species, high levels of iron may promote the development of neurodegenerative diseases such as Alzheimer's and Parkinson's. Thus, the guttiferone might be a strategy to avoid such diseases (García-Beltrán et al., 2017) (Carocci et al., 2018) (Figueredo et al., 2011).

Guttiferones are still in the process of characterization, and evaluating their toxicity before starting using them in therapy is an essential step. Terrazas et al. (2013) approached the topic by studying the genotoxic effects of guttiferone A on a number of different cell types isolated from Swiss mice cells (Table 3). The results showed that guttiferone A might act as a mutagenic and genotoxic agent (Terrazas et al., 2013). The work of Terrazas et al. (2013) alerts to the danger of consuming excessive quantities of plants with high concentrations of guttiferone A. One example is *Garcinia achachairu* Rubsy, used by the local medicine of Brazil, Bolívia, and other countries to treat gastrointestinal disorders and inflammatory

diseases. The researchers recommend caution on using the plant as a medicine because of the genotoxic effects that it may cause.

Besides HIV, other viruses might be affected by the actions of guttiferones, for example in the case of guttiferone K in an hepatocellular carcinoma (HCC) condition, which one of the main causes is chronic viral hepatitis. Shen et al. (2016) has shown that the guttiferone inhibits cell motility and metastasis, however, there is no mention of a possible direct antiviral effect against hepatitis viruses. Indeed, a study already supported an antiviral action of the botanical origins that contains high levels of guttiferones, such as *G. multiflora* against herpes viruses and influenza A and B viruses (Lin et al., 1999), and *Garcinia kola* against the Ebola virus (David, Toluwase and Oluwasegun, 2017).

5. Toxicological aspects

Guttiferones, as a recently studied class of components, have insufficient data to allow a discussion on its toxicity. Nonetheless, the major group of chemical substances that guttiferones are a part of – the benzophenones – were already screened for its toxicity that may add some knowledge on guttiferones as well.

The benzophenone class has at least 300 members that share a phenol-carbonyl-phenol skeleton. Within these members, structural differences lead to a variety of actions and possible toxicities. Most of the studies presented in this review showed little toxicity of the guttiferones, as polyprenilated benzophenones, to mammalian cells (Wu, Long and Kennelly, 2014). However, there is a large number of reports about the biological and environmental risks of benzophenones used in the production of sunscreens, anti-aging products and other personal care substances as substances that can protect from photodegradation, being considered carcinogenic and endocrine disruptor compounds (Downs et al., 2021) (Wnuk and Kajta, 2021).

The benzophenones presented in these products were found accumulated in biological samples of urine, blood, breast milk, in the placenta, which are worrying for the effects these substances may have in the human body (Mao et al., 2022). Benzophenone-3 for example induces phototoxicity in keratinocytes by increasing pro-inflammatory mediators, impairs hormones distribution in men and women, and induces neurotoxicity, outcomes summarized by Wnuk and Kajta's (2021) in their review.

One difference between the benzophenones from which guttiferones are derived and whose actions are beneficial to health and benzophenones used in the cosmetics industry that

may be carcinogenic is their origin: the first being naturally occurring substances and the later mostly synthetic (Surana, Chaudhary, Diwaker and Sharma, 2018). This suggests that the naturally occurring benzophenones go through essential processing steps that turns the compounds less toxic to the organisms. Even though natural products are in most cases safe, it is important to conduct more studies to screen their toxicity and present the best way of their use as biological active compounds.

6. Challenges and new perspectives

The main challenges in using natural compounds for therapeutic purposes are short stability and low bioavailability due to their lipophilicity, which drives the need to administer higher doses that can lead to toxic effects. New techniques in formulation science, such as nanotechnology, can be helpful as a strategy to overcome these challenges (Watkins et al., 2015).

Nanotechnological delivery systems can either encapsulate natural products or have them into their composition. By encapsulating natural products on nanoemulsions, such as Fasolo and coworkers achieved with a benzophenones-rich Brazilian red propolis extract, skin permeation can be enhanced, ideal for topical application, for example (Fasolo et al., 2020). Plant extracts rich in benzophenones can be used in the synthesis of non-biodegradable gold and silver nanoparticles (AuNPs and AgNPs, respectively) as stabilizing and capping agents due to their ability to reduce Au^{3+} and Ag^{+} ions to Au^{0} and Ag^{0}, turning it into a less toxic, more biocompatible and bioavailable nanostructure (Andra et al., 2019) (Sangaonkar et al., 2018; Kureshi et al., 2021).

Therefore, by uniting the complete understanding and characterization of guttiferones - their biological actions and toxicity aspects - with the application of these compounds into reliable formulations such as nanostructures, significant advances can be expected in medical practice supported by alternative therapies with products of natural origin.

7. Conclusion

Guttiferones, molecules that belong to the polycyclic polyprenylated acylphloroglucinols (PPAPs) class, are found in abundance in plants from the genus Garcinia. Each species has one type of guttiferone in evidence, as in the case of guttiferone A (*G. brasiliensis*, *G. gardneriana*), E (*G. xanthochymus*, *G. multiflora*), K (*G. madruno*, *G. gummi-gutta*) and others.

This review summarizes the chemical structure, naturally occurring, pharmacological activities, toxicity, and possible future applications of certain guttiferones. Indeed, guttiferones have therapeutic actions in different situations, generally acting in a dose-dependent manner, with few situations in which this pattern is not observed. Through the presented material, the respective molecular characteristics of each type of guttiferone as well as procedural information on plant parts, types of extract, and concentrations used by each study can be accessed practically and visually, making the process of understanding the general context of research more agile.

Credit author statement

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Declaration of competing interest

The authors declare no conflicts of interest.

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