Jejurkar and Chavan
*Future Journal of Pharmaceutical Sciences* (2023) 9:95
https://doi.org/10.1186/s43094-023-00547-4

Future Journal of Pharmaceutical Sciences

REVIEW

Open Access

# Therapeutic benefits of gossypin as an emerging phytoconstituents of *Hibiscus spp.*: a critical review

Gayatri Jejurkar[1*] and Machindra Chavan[1]

## Abstract

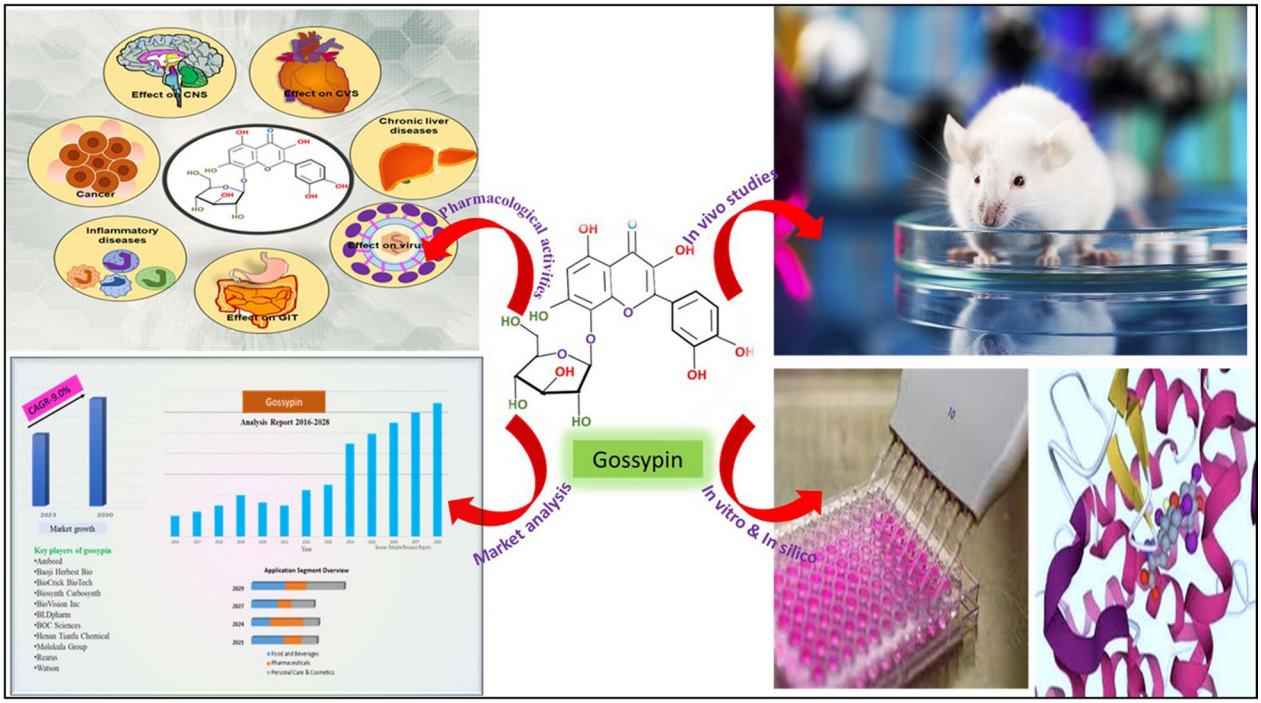
**Background** Flavonoids are one of the crucial secondary metabolites as several functions are carried out by flavonoids, including regulating cell growth, luring insects and pollinators, and defending against biotic and abiotic stressors. They are found in fruits, whole grains, vegetables, spices, tea, wine, herbs, and seeds. More than 4000 flavonoid compounds have been discovered and extracted through different techniques. Most flavonoids are frequently utilized in pharmaceuticals, nutraceuticals, cosmetics, and other products. A flavonol glucoside called gossypin is the primary phytochemical of herbs that comes under the "Malvaceae" family and can be found in many species, including *Hibiscus esculentus, Gossypium indicum*, and *Hibiscus vitifolius*, all have it in their flowers. Gossypin shows not only significant pharmacological activities but also a defence mechanism and protects against pathogens, UV radiation, etc. It has drawn much interest from researchers and scholars due to its benefits of few adverse effects, high efficacy, and simple preparation. Thus, the current review focuses primarily on the pharmacological accounts of gossypin in various acute and chronic diseases. The various assays and animal studies conducted in the past supported gossypin effects as supporting the concept of the objective of the title. The review also highlights various patents filled on gossypin's importance and current market scenario.

**Conclusion** Therefore, the technical contents based on pharmacological activities, patents and current market scenario provided in this paper for the improvement of research in numerous scientific fields will be helpful to researchers for suitable alternative designs of gossypin in various disorders.

**Keywords** Gossypin, Pharmacological activities, Cell lines, Animal models, Patents, Market research

*Correspondence:
Gayatri Jejurkar
gayatrijejurkar87@gmail.com
Full list of author information is available at the end of the article

**Graphical abstract**




## Background

Medicinal plants have always been crucial to the advancement of human health. More than 80% of the global population, according to the World Health Organization, is dependent on healing plants to preserve their wellness and alleviate illnesses [1–3]. More than 8,000 different types of medicinal herbs are native to India, as reported by the Botanical Survey of India. Traditional medical practices have a long history in the nation, and current study on medicinal plants is ongoing due to their numerous advantages [4]. The primary chemical components of plants, present in leaves, fruits, flowers, seeds, and occasionally even the entire herb, are called phytochemicals [5, 6]. Terpenoids, flavonoids, glycosides, phytosterols, saponins, carotenoids, alkaloids, aromatic acids, protease inhibitors, essential oils, and organic acids are the main groups of phytoconstituents (PCs) [7, 8]. They can diagnose, treat, and ultimately eradicate all chronic and degenerative diseases affecting human beings. The metabolites also offer defensive mechanisms (direct or indirect) against infections or hazardous illnesses, including antibacterial, anthelmintic, anticarcinogenic, anti-inflammatory, antigenotoxic, antimutagenic, antioxidative and antiproliferative [9–11]. The traditional plant has distinct pharmacological effects on the human body [12]. As a result, the evaluation concentrated on addressing the demands of society to determine the effectiveness of traditional treatments. The review aims to highlight the specifics of pharmacological activities along with in vitro and in vivo research of medicinal herb gossypin (GOS) using previous studies.

### Overview of flavonoids

Cereals, fruits, nuts, herbs, vegetables, stems, flowers, as well as seeds are the most common sources of flavonoids, which are secondary metabolites [13]. The therapeutic efficacy and biological activity of these parts of plants are due to the PCs contained in them. Ten thousand flavonoids have been found and derived so far [13, 14]. Most flavonoids are commonly used as pharmaceuticals such as anthocyanidin and proanthocyanidin, isoflavone, anthocyanins, and gossypin [15]. The potential health advantages offered by the antioxidant capabilities of these polyphenols have sparked recent interest in these substances. To function as antioxidants, hydroxyl groups either bind metal ions or scavenge free radicals [16]. Flavonoids are thought to be dietary components with health-promoting properties. Also, the human body's defence-enhancing enzyme pathways can be activated by flavonoids [17]. Many plant species contain flavonoids,

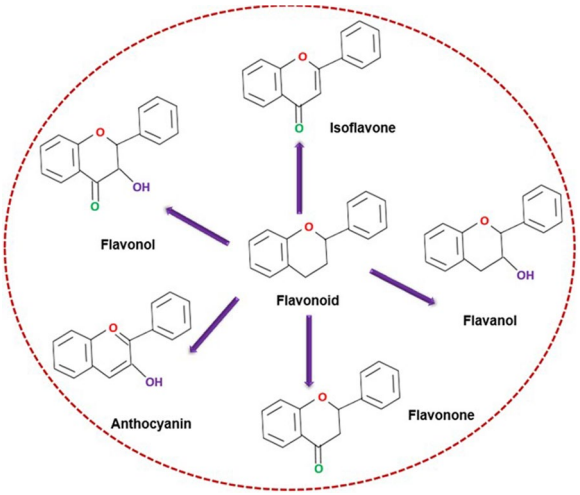



**Fig. 1** Basic flavonoid structure and their various types (Own creation)

including *chamomile*, *ginkgo biloba*, *hibiscus*, and others (Fig. 1). Gossypins present in several plant species with a variety of biological functions because of its structural makeup [18]. It has been demonstrated to inhibit carcinogenesis, angiogenesis, and other processes. Gossypin thus receives much interest from researchers and scholars [19].

## Structure and pharmaceutical importance of gossypin

Gossypins [2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4-oxo-4H-chromen-8-yl b-D-gluco-pyranoside] (Fig. 2) with a molecular formula ($C_{21}H_{20}O_{13}$), a flavanol glucoside [20], are primarily found in flowers and roots of

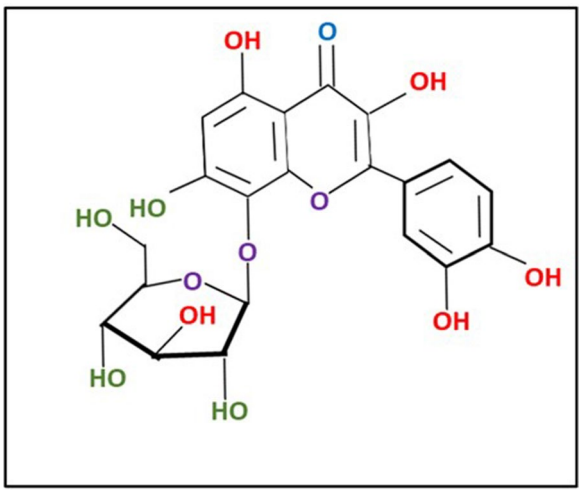


**Fig. 2** Basic structure of gossypin (Own creation)

numerous *hibiscus* species, including *H. esculentus*, *H.vitifolius*, and *G. indicum* [21, 22] belonging to the "Malvaceae" family. Gossypin is like a gossypetin in terms of function [23]. It indicates physical properties including yellow crystalline solid powder, high melting point (229–230 °C), and markedly soluble in water. The existence of the glucose moiety makes the compound more soluble in water and less soluble in alcohol and other solvents [24]. Also, it is more stable than other phytoconstituents due to structural arrangements.

## Pharmaceutical importance of gossypin

There are between 50,000 and 80,000 flowering plant species used for medicinal purposes worldwide. These herbs are supplemental or alternative medicine. For the development of new drugs, studies on these medicinal plants that include pharmacological and toxicological assessments are crucial globally. Since there are many different types of plants in India, there is a significant chance that their economic value can be maximized by developing technologies for their cultivation and processing [25, 26]. According to statistics, there are 18,000 species of higher plants in India with various phytogeological and ecological zones including Himalayas region, Karnataka, Maharashtra, Tamil Nadu, etc., of which around one-third are essential for health care and the economy [27]. However, less emphasis on therapeutic benefit of cotton metabolites containing rich oil and protein, which has medicinal value, might lead to the new way for a more thorough application of cotton products [28]. This is partially because of extensive interest in cotton as an economically viable crop for vegetable oil, feedstuff, and textile fibre. Gossypin is used in various fields, including those related to chemicals, medicine, and others (Fig. 3). As it can prevent cell proliferation, gossypin is employed in the pharmaceutical sector to develop the anticancer medications. Gossypin is a natural pigment used in the chemical industry as a colourant in soaps, cosmetics, as well as dyes; another uses are insecticide and antioxidant. Gossypol, gossypetin, gossypin, and gossypose are a few examples of the many metabolites or defensive substances produced by cotton plants [29, 30]. Gossypin can also be employed as an ether sizing agent belonging to the technical domains of preparing sizing agents [31]. Compared to the parent compound, Nair demonstrated that gossypin nanoparticle formulation successfully halted colony formation and growth in vitro. Gossypin may limit the proliferation and invasion of tumour cells and vascular permeability induced by VEGF and tumour neovascularization, causing cell cycle arrest [32]. Additionally, the gossypin has physical characteristics like marked solubility, increased bioavailability, and long-term effectiveness [33]. Thus, this phenomenon can be

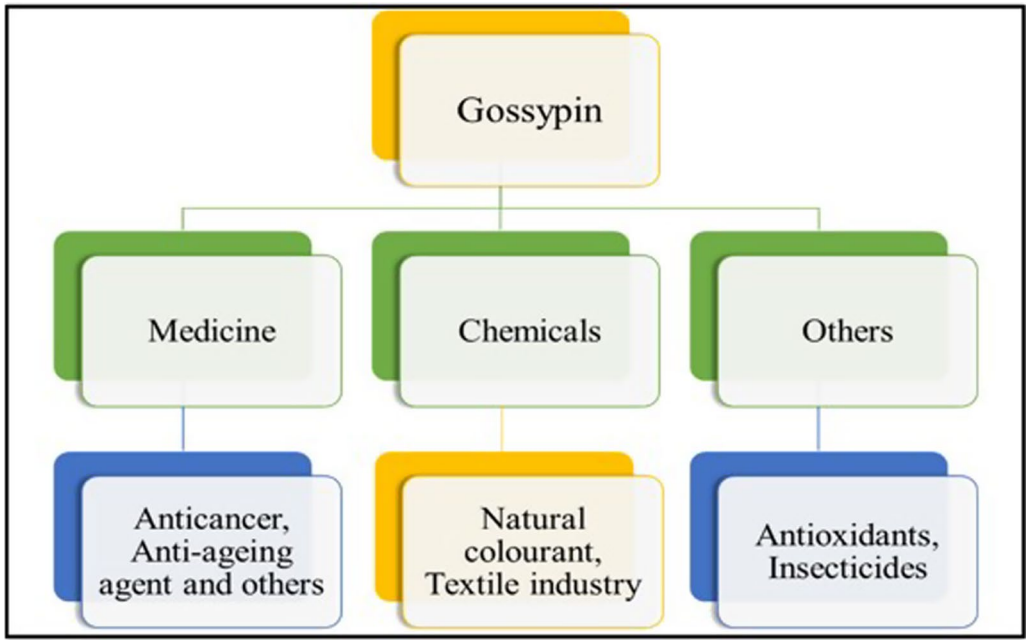



**Fig. 3** Segments of gossypin in the pharmaceutical industry (Own creation)

used in different gossypin formulations. NMR spectra by GIAO approximation revealed GOS-SWCNT structure, which appears the number of active sites in GOS-SWCNTs that have the most activity at indicated model proved by Shabanzadeh. This compound offers an atomistic examination of the GOS–SWCNT method and its use in ongoing pharmacological research [34]. Overall, gossypin and its derivatives perform vital economic part in the development of the pharmaceutical domain.

#### Proven pharmacological activities of gossypin

Gossypin has attracted a lot of attention from academics and researchers because it not only has strong pharmacological effects but also has minimum adverse effects and easy preparation. The purpose of this part is to give a theoretical foundation for the clinical use of gossypin by briefly describing the pharmacological effects (Fig. 4) and mechanism of the drug [35] (Table 1).

#### Limitations of gossypin and solutions to overcome

Folklore systems originated in ancient times and are still in use today. According to Shrikumar, Complementary and Alternative Medicine (CAM) systems are a miracle for herbal and conventional medicine [36]. Moreover, certain factors constrained the usage of gossypin are as follows:

- Gossypin is considerably more soluble in water and less in anhydrous organic solvents. It is challenging to obtain it completely free of mineral matter due to this property [37].
- Another obstacle to extracting these compounds is that the flavonoids are typically labile, subjecting them to significant levels of chemical structure degradation or alteration and subsequent activity loss during purification [38].
- Isolation and separation of gossypin from plant species are somewhat difficult as it was observed that very few ionic compounds were identified. Awouafack noted more moderately polar polyphenols, including certain terpenoids, steroidal chemicals, and gossypin [39].
- Gossypin-powdered extract must be stored and handled carefully because it is hygroscopic and incompatible with strong oxidizers.
- For these herbal bioactive, potential side effects include skin, eye, and respiratory irritation [40].

#### Solutions to overcome these issues

By increasing solubility, bioavailability, stability, also bioactivities of phytochemicals, nanotechnology has the potential to help overcome these obstacles [41]. The proniosomal drug delivery strategy, according to Jampala

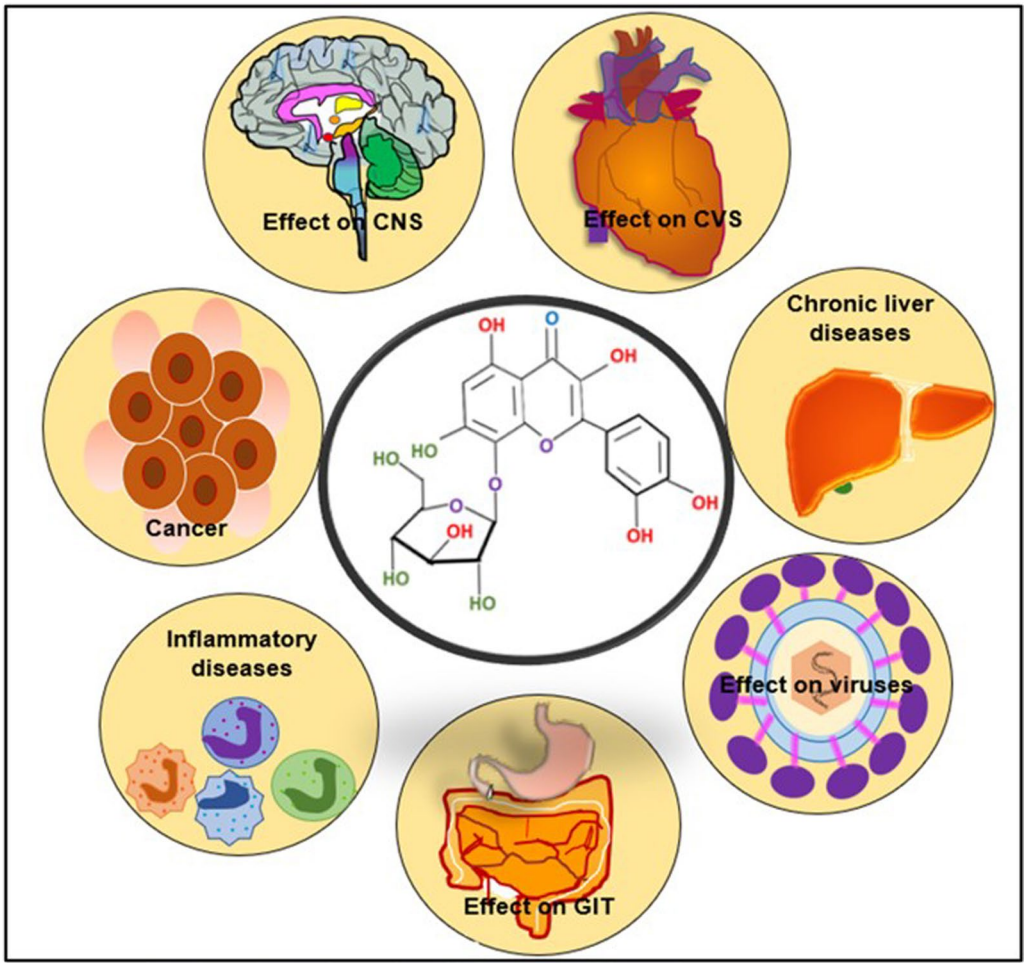



**Fig. 4** Gossypin uses in variety of diseases (Own creation)

and colleagues, can improve the flow into the skin and produce the optimal sustainability effect of GOS. Considering this, using proniosomal gel to deliver gossypin topically for managing melanoma treatment could be useful [42]. Additionally, the liposomal-GOS formulation provides mice prevention from PTZ kindling. Liposomal-GOS treatment dramatically slowed the advancement of kindling in mice, making it an excellent candidate to manage the oxidative stress that occurs during epilepsy as well as the development of seizures [43].

Gossypin is more stable than most other naturally occurring chemicals owing to the existence of the -OH group in their structure, which stabilizes the molecule and prevents it from interacting with other substances. The methods, including high-performance liquid chromatography (HPLC), ion-exchange column chromatography, mass spectroscopy (MS), nuclear magnetic resonance (H1NMR), liquid chromatography-mass spectroscopy (LC–MS), high-performance thin layer chromatography (HPTLC), can be suitable techniques used to isolate and study the chemical composition of gossypin [44]. The low extraction yield of flavonoids produced by the existing conventional separation and purification procedures typically not able to justify the greater cost of extraction. The extraction yield of flavonoids could be increased by optimizing the conditions using response surface methodology over these conventional techniques. Diverse tactics are used to overcome these restrictions [45, 46].

### In vitro and in vivo investigation of gossypin

In vitro studies of gossypin produced from *Hibiscus* species were carried out using cell lines or assays to determine the bioactivities. The description of the studies is shown in Table 2.

**Table 1** Gossypin activities along with study models

| Pharmacological activities | Mechanism of action | Cell lines/assays/animal models | Result |
|---|---|---|---|
| Antidiabetic | Decreased blood glucose and HbA1c levels also increase haemoglobin and plasma insulin levels | Albino Wistar rats<br>Streptozotocin-induced experimental diabetes in rats | Reduced blood sugar and HbA1c levels, as well as higher levels of plasma insulin and haemoglobin [51]<br>Gossypin has potent antidiabetic activity [52] |
| Anti-inflammatory | COX-2 and lipoxygenase inhibition played a role | Carrageenin-induced rat hind paw oedema model. Male Wistar rats<br>Male Swiss rat. Carrageenin was injected into the right hind paw oedema model<br>Sonicated sheep platelets | Procumbentin and gossypin have less potency than rofecoxib but still selectively inhibit COX-2 [53]<br>Most effective for inflammation, while leucocyanidol had minimal impact [54]<br>Inhibition of lipoxygenase might be crucial for this activity [55] |
| Anticancer | Inhibits U251 cell proliferation through Cell division cycle 25C (Cdc25C) and Chk1 | HT 29 and K 562 cell lines<br>U251 cell lines<br>MTT assay | Inhibit the DNA replication enzymes, topoisomerase I and II [56]<br>Cdc25C tyrosine phosphatase triggered arrest of cell cycle during G2/M phase by activating checkpoint kinase 1 (Chk1) [57]<br>Gossypin inhibit NF-kappa B, Hence, function in carcinogenesis, inflammation, and angiogenesis suppression [58] |
| Analgesic | Involvement of opiate receptors | Acid-induced writhing in mice | Gossypin-naloxone showed that opiate receptors are involved in the analgesic activity of gossypin [59] |
| Antiallergic | Inhibiting anti-pruritics, anaphylaxis reactions | Synthetic poly sulphonated naphtyl urea, on the mast cell-mediated allergy paradigm | Gossypin and suramin decrease allergic reactions caused by mast cells [60] |
| Antiviral | Against plaque formation of HSV-2 and HSV-1 | In vitro plaque reduction assay in Vero cells | Therapeutic potential for managing and avoiding herpes simplex virus infections [61, 62] |
| Antioxidant | In vitro lipid peroxidation inhibitory potential | DPPH assay | At a 100 µg/ml concentration, GOS and BHT significantly block the DPPH radical. Nitric oxide, superoxide, and hydroxyl radical scavenging effect of GOS at the same concentration [63] |
| Effect on CNS | Affecting both GABA aminergic and glycine inhibitory mechanisms | Sprague–Dawley rats of either gender. Global cerebral I/R model<br>Maximal electroshock convulsive techniques in mice | Dose-dependent neuroprotective efficacy [64]<br>Reduced the tonic extensor convulsion [65] |
| Effect on CVS | Reduces the total cholesterol quantity and raises LDLR, it is not dependent on SREBP-2 while dependsupon activation of ERK | HepG2 cells<br>H9c2 cell and Sprague–Dawley (SD) | Dose-dependently decreased the total cholesterol concentration. Low-density lipoprotein receptor (LDLR) protein expression increased, no effect on HMG-CoA reductase. Furthermore, did not impact the quantity of nuclear SREBP-2 [66]<br>Normalized elevated LDH, Tn-I and CK-MB levels. Enhanced SOD, GSH, TNF-α, NF-kB mRNA, IL-6, and IL-1 expression levels and reduced MDA quantity, gossypin regulates ISO administration in cardiac tissue [67–69] |
| Effect on gastric system | Delay small intestinal transit via opiate and alpha-2 adrenergic receptors | Wistar Rat<br>In-vitro everted gut sac model | In a dose-dependent way, all 3 flavonoids hindered the small intestine transit. [70, 71]<br>Other bioflavonoids like methyl hesperidin, gossypin, diosmin, chrysin and quercetin reduced nitrendipine transport rate[72] |
| Toxicity study | Prevents beta-amyloid induced toxicity, protects against glutathione peroxidase | Mice<br>Primary cultured rat cortical cells. Cell-free assays<br>Rat hepatocytes | Gossypin delivered in PEG-300 provided better protection against SM toxicity [73–75]<br>It prevented xanthine/xanthin oxidase or D,L-buthionine (S,R)-sulfoximine induced oxidative neuronal distortion [76]<br>Reduced the release of alanine amino transferase [77] |

**Table 2** In vitro studies of gossypin

| Study title | Assay/cell lines | Outcomes |
|---|---|---|
| Topical drug delivery of gossypin from proniosomal gel formulations: *in-vitro* efficacy against human melanoma cells | The MTT assay | GOS-loaded gels (GPG) showed viability of cell 14.9% ± 2.3% compared to 16.1% ± 1.0% for free gossypin in A-375 human melanoma cells. Further being stored for 90 days, the %EE or PS of GPG didn't change significantly [42] |
| Neuroprotective effect of Gossypin on glutamate-induced excitotoxic neuronal death in SH-SY5Y cell line | Human SH-SY5Y neuroblastoma cells | Gossypin treatment reduced MDA levels and increased GSH and SOD concentrations. Protective role in neurotoxicity caused by glutamate [78] |
| Gossypin Protects Primary Cultured Rat Cortical Cells from Oxidative Stress-and J3-Amyloid-Induced Toxicity | Primary cultured of rat cortical cells. Cell-free assays | Inhibited oxidative stress as well as Aβ-induced toxicity, suggesting gossypin's antioxidant characteristic [76] |
| Gossypin as a Novel Selective Dual Inhibitor of v-raf Murine Sarcoma Viral Oncogene Homolog B1 and Cyclin-Dependent Kinase 4 for Melanoma | In vitro melanoma cell lines | Inhibited human melanoma cell proliferation, BRAFV600E and CDK4 kinase activities and revealed GOS as a new drug with double inhibitory actions to cure skin cancer. Molecular docking confirmed direct linking of GOS with both kinases [79] |

**Table 3** In vivo studies of gossypin

| Study title | Animal models | Outcomes |
|---|---|---|
| Evaluation of liposomal gossypin in animal models of epilepsy | Swiss albino mice were used. PTZ-induced seizures and the ICES test in rodents was carried out using 2 dosages, 2.5 and 5 mg/kg of GOS | Gossypin significantly increased the seizure threshold and the latency to generalized seizures. MDA levels increased, glutathione levels dropped, and mice's kindling process was slowed at doses of 2.5 and 5 mg/Kg [43] |
| Protective Effects of Gossypin in Colchicine-induced Cognitive Dysfunction and Oxidative Damage in Rats | The Male Wistar rats were taken, and they received oral solutions of GOS (10 or 20 mg/kg) upto 3 weeks and intracerebroventricular injections of colchicine. The Morris Water Maze was used to measure the activity of gossypin, Using the Schrodinger suite, a docking interaction study was conducted | The latency period indicated an insignificant reduction in the gossypin-treated group. However, increase in island entries. Overall, Gossypin demonstrated a vigorous in silico interaction with AChE and a minor cognitive enhancement characteristic [33] |
| Prophylactic Effect of Gossypin Against Percutaneously Administered Sulfur Mustard | 25–30 g Swiss albino female mice were used | Gossypin administered with PEG-300 (8.0 folds) provided greater defence against the systemic toxicity of SM than DMSO (5.7 folds). For seven days, a considerable reduction in weight was seen along with a significant rise in RBC and Hb [75] |
| Gossypin, a Flavonol Glucoside Protects Pancreatic Beta-Cells from Glucotoxicity in Streptozotocin-Induced Experimental Diabetes in Rats | Rats, male Albino Wistar, were grouped into 4 groups ($n=6$) | When given orally, GOS dramatically increased antioxidants and decreased lipid peroxides, NO, IL-1, and nuclear NF-B p65 units in pancreatic tissue in diabetic rats [80] |
| Effects of Gossypin on Fracture Healing in Experimental Femur Fractured Mouse Mechano-Bioregulatory Model | Male Mus musculus BALB/c 28 mice have been chosen. An open fracture model was created for this estimation | In groups 3 and 4, GOS sufficiently slowed bone resorption and reduced inflammation in mice with femoral fractures. Biomechanical research revealed sufficient hardness levels and high braking force thresholds [81] |

### Gossypin's in vivo studies

This research examined the bioactivities of the phytochemical using animal models. The description of studies is shown in Table 3.

### Patents filed on gossypin

Filing and approving patents provide conclusive evidence of an item's commercial interest. In this regard, the researcher has received a few patents for their inventive work and study on gossypin PCs. The patent gives exclusive rights to innovation, which also prevents others from misusing it. A few of the patents, which are granted, are discussed in Table 4.

### Market analysis of gossypin

The gossypin market analysis provides information on market size, growth rate, segmentation, and a

**Table 4** Patents filed on gossypin

| Inventor | Application/patent number | Summary along with references | Patent/publication date |
|---|---|---|---|
| Marc Winnefeld<br>Sabine<br>Torsten Schläger<br>Hagemann<br>Elke Grönniger<br>JörnSöhle<br>Katrin Schmidt | WO2016034400A1 | The Chinese scientists patented current research, which refers to dermatological or cosmetic formulations containing active substances for curing and protecting the skin, particularly skin ageing caused due to intrinsic and external causes. Gossypetin/gossypin resolved this problem to treat and prevent skin ageing, as well as damaging effects of UV radiation [82] | 2016-03-10 |
| Mei Qingbo Sheng Haifeng Meng Haoying | CN106120336A | The invention was patented in 2016 and disclosed the preparation method of a kind of gossypin ether sizing agent belonging to the sizing agent preparing the technical field.There are some beneficial impacts of the invention: The preparation procedure of current invention is simple, has no residue for safety or environmental protection, and causes no harm to fibrous tissue by adding any oil-dissolving solvent. Improved interface bond strengthby 25–28%, effective resolution of the weak fibre pliability, easily created lousiness, and broken end problems [31] | 2016-11-16 |
| Lai Yuekun Li Shuhui Huang Jianying Ge Mingzheng Zhang Keqin | CN104294594B | Another approval was given to research work that disclosed the preparation method of the super thin fabric face of a water and oil repellant. The method comprises the 3 steps: (1) Bafta was weighed, and a gossypin macromole evocating agent was made; (2) grafted monomers GMA were then added to the gossypin macromole evocating agent of the preparation. (3) In gossypin and the low-surface-energy monomer generation acylation reaction of the grafting GMA of the cellulose surface rich in hydroxyl of the above-mentioned preparation.The procedure has a moderate reaction condition, stable at room temperature, and is easy to use. It can also ensure good superhydrophobicity and grease resistance. Hence, the method was found to be suitable for preparation of fabric face [83] | 2016-05-18 |
| Wang Shuhua Jia Husheng Hou Wensheng Dai Jinming Gao Xiaoyue Liu Jinlong | CN102633249B | The object of the invention relates to the situation for background technology; employing gossypin as acarbon source, the carbospherewas synthesized in fast degradation carbonization to improve preparation efficiency and the quality of carbosphere. The method of creating carbon microspheres quickly using cotton cellulose is the focus of the present invention. The approach is suitable because it has the benefits of an innovative process, rapid speed, less used equipment, abundant raw material resources, low price, and less energy required by a carbonization process. This technology decreases environmental pollution by recycling waste textiles into fuel and creating a road asphalt modifier that fully employs coal [84] | 2014-04-02 |

**Table 4** (continued)

| Inventor | Application/patent number | Summary along with references | Patent/publication date |
|---|---|---|---|
| Han JinNiu Ying Wang Xiaoyang Zhou Yanping Yuan Hailong | CN105228658B | The patent was registered in 2018 on research work "A kind of medical dressing hydrogel compound fabric and its preparation method and application". Formulation technique described as the initiator and n-isopropyl acrylamide were immersed in a solution and foamed with nitrogen gas; Gossypin performs an initiation reaction in an initiator solution; following that gossypin soaks in a solution containing n-isopropyl acrylamide and dimethylformamide; this causes polymerization and yields poly-N-isopropyl acrylamide-gossypin; finally, this product and alginate were mixed. After the solvent is eliminated, a hydrogel fabric is obtained for medical dressings. This hydrogel is primarily used to stop bleeding and restore damaged tissue in both acute and chronic wounds [85] | 2018-04-20 |

comparison of factors or challenges that could impact the market's future. Because of the increased need of herbal products, especially in nutraceutical and pharmaceutical industries, the GOS market is now expanding. Gossypin applications are becoming more varied, spanning from skincare to cancer treatment, further boosting the drug's market growth [47]. The market still has difficulties due to low extraction yields and a scarcity of raw materials. To optimize the potential of gossypin, it is crucial for key stakeholders and industry professionals to examine creative solutions to these problems. Gossypin is used in a variety of industries, including those related to chemicals, medicine, and others. Due to its capacity to impede cell proliferation, gossypin is utilized in the pharmaceutical sector in the development of anticancer medications. Gossypin is a natural pigment used in the

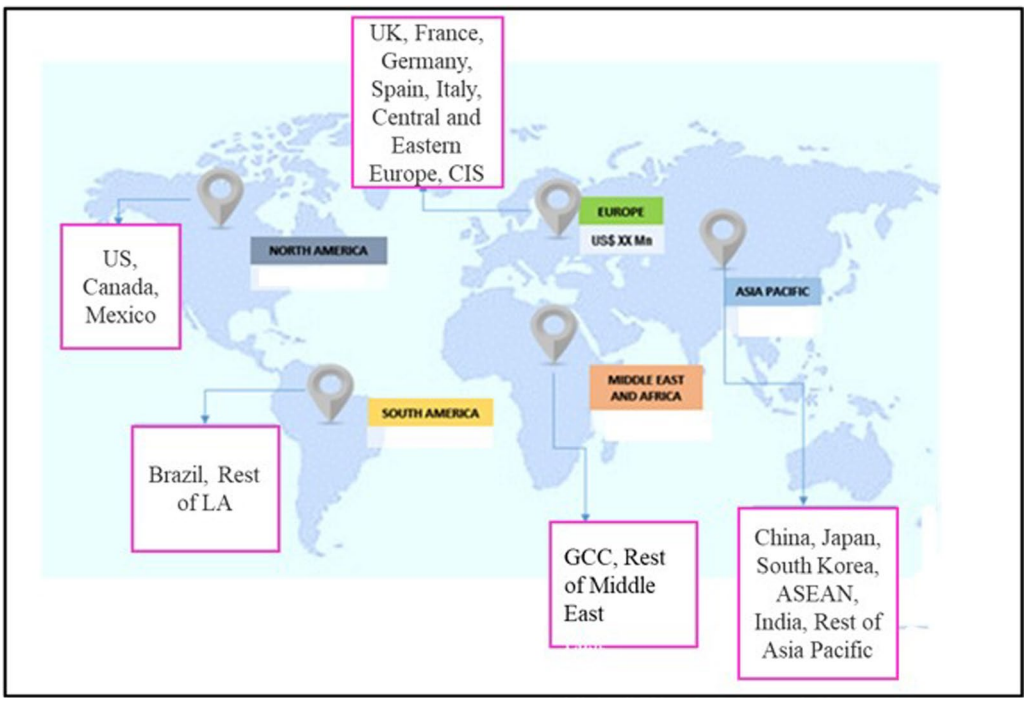



**Fig. 5** World distribution of gossypin (Source: Internet + Own) [50]

chemical industry to colour cosmetics, soaps, and dyes. Gossypin can also be used as an insecticide and antioxidant, among other things. The market for gossypin has expanded owing to its variety of applications [48]. The areas that notably covered gossypin market are:

- North America
- Asia Pacific
- Europe
- Middle East and Africa
- Latin America (Fig. 5).

### Market players (company) in the gossypin

Gossypin presents in cotton plants with possible medical benefits. Some of the major participants in the gossypin market include Ambeed, BioCrickBio Tech, Baoji Herbest Bio, Henan Tianfu Chemical, BiosynthBLD pharm, BioVision Inc, Molekula Group, BOC Sciences, Rarus, Carbosynth, and Watson (Fig. 6). These organizations can contribute to the expansion of the GOS market by diversifying their geographic reach and investing in R&D to find new and innovative therapeutic uses [49, 50].

## Conclusion

Many of the drugs utilized in the modern medical system originated from natural sources. Furthermore, traditional medicines were the primary form of healthcare for most populations in Asia and Africa, e.g., China, Japan, South Korea, India, etc. Due to the perception that they have fewer adverse effects and greater effectiveness, herbal medications are utilized worldwide to cure various acute and chronic disorders. Gossypin, a bioflavonoid, is naturally derived from *Hibiscus* species belonging to the Malvaceae family. Due to their structural makeup, they own a wide spectrum of bioactivities. Further, they also utilized in textile, cosmetics, and nutraceutical industries. Some identified biological activities were proved using animal models, cell lines or assays, supporting the concept. Overall, this review presented a database for beneficial effects, current scenarios and market analysis of gossypin, which will be attention for researchers in the future.

## Future perspectives

The herbs are supplemental or alternative medicine. For the development of new drugs, studies on these medicinal plants that include pharmacological and toxicological


**Fig. 6** Analysis report of gossypin along with the key players (Source: Internet + Own) [50]

assessments are crucial globally. Still some research needs to be done to evaluate the efficiency of herbal plants. The significant obstacle is the lack of an animal model that accurately imitates the histologic and immunophenotypic features of pharmacological actions. Thus, randomized controlled clinical trials are required in future research for the systematic evaluation of such herbs in terms of efficacy and safety in humans. To enhance the effectiveness of the treatment, molecular targets that control several critical pathogenic variables can also be targeted. More investigations are required to advance herbs provided nano-cosmetics, nanotechnology to ensure that nano-scaled plant extract-loaded formulations continue to be the excellent and unique option in the upcoming era. Considering the enormous potential that plant-based medications must treat a wide range of illnesses, it is now possible to state that much more knowledge and experience are still needed in this field.

**Abbreviations**

| | |
|---|---|
| PCs | Phytoconstituents |
| GOS | Gossypin |
| NMR | Nuclear magnetic resonance |
| SWCNT | Single-walled carbon nanotubes |
| Cdc25C | Cell division cycle 25C |
| Chk1 | Checkpoint kinase 1 |
| LDLR | Low-density lipoprotein receptor |
| SD | Sprague–Dawley |
| CAM | Complementary and Alternative Medicine |
| PEG | Polyethylene glycol |
| HPLC | High-performance liquid chromatography |
| MS | Mass spectroscopy |
| LC-MS | Liquid chromatography-mass spectroscopy |
| HPTLC | High-performance thin-layer chromatography |
| GPG | Gossypin-loaded gels |
| SM | Sulphur mustard |
| UV | Ultraviolet |
| VEGF | Vascular endothelial growth factor |
| GIAO | Gauge-independent atomic orbital |
| HbA1c | Glycated haemoglobin |
| COX-2 | Cyclooxygenase 2 |
| DNA | Deoxyribonucleic acid |
| MTT | 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide |
| HSV | Herpes simplex virus |
| BHT | Butylated hydroxytoluene |
| DPPH | 2,2-Diphenyl-1-picrylhydrazyl |
| GABA | Gamma-aminobutyric acid |
| I/R | Ischemia-reperfusion |
| HMG-CoA | β-Hydroxy β-methylglutaryl-CoA |
| SOD | Superoxide dismutase |
| GSH | Glutathione |
| TNF-α | Tumour necrosis factor alpha |
| NF-kB | Nuclear factor kappa B |
| IL | Interleukin |
| ISO | Isoprenaline |
| PTZ | Pentylenetetrazole |
| MDA | Methylenedioxyamphetamine |
| RBC | Red blood cell |
| NO | Nitric oxide |
| R&D | Research and Development |

**Acknowledgements**
We would like to thank to all suppliers for offering the required materials and also reagents for research purposes.

**Author contributions**
GJ contributed to the design of the study; GJ and MC collected the samples; GJ and MC performed the experiments and analysis the data; GJ and MC drafted the paper; all authors read and approved the final manuscript.

**Funding**
Not applicable.

**Availability of data and materials**
The data that support the findings of this study are available from the corresponding author, upon reasonable request.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
The authors declare no conflict of interest.

**Competing interests**
The authors declare that they have no competing interests.

**Author details**
[1] Amrutvahini College of Pharmacy, Sangamner, Ahmednagar, Maharashtra 422608, India.

Received: 15 July 2023 Accepted: 18 October 2023
Published online: 26 October 2023

**References**

1. Raju GS, Moghal MR, Dewan SMR, Amin MN, Billah M (2013) Characterization of phytoconstituents and evaluation of total phenolic content, anthelmintic, and antimicrobial activities of Solanum violaceum Ortega, Avicenna. J Phytomedicine 3(4):313–320
2. Salmerón-Manzano E, Garrido-Cardenas JA, Manzano-Agugliaro F (2020) Worldwide research trends on medicinal plants. Int J Environ Res Public Health 17(10):3376. https://doi.org/10.3390/ijerph17103376
3. World Health Organization report (2022) https://www.who.int/news/item/25-03-2022-who-establishes-the-global-centre-for-traditional-medicine-in-india.
4. Biotonical survey of India, https://scroll.in/article/954167/india-is-home-to-over-8000-species-of-medicinal-plants-and-theyre-increasingly-under-threat.
5. Altemimi A, Lakhssassi N, Baharlouei A, Watson DG, Lightfoot DA (2017) Phytochemicals: extraction, Isolation, and identification of bioactive compounds from plant extracts. Plants Basel Switz 6(4):42. https://doi.org/10.3390/plants6040042
6. Oz AT, Kafkas E (2017) Phytochemicals in fruits and vegetables. In: Superfood and functional food: an overview of their processing and utilization, V. Waisundara and N. Shiomi. Eds InTech 2017. https://doi.org/10.5772/66987
7. Bhattachar S (2011) Natural antimutagens: a review. Res J Med Plant 5(2):116–126. https://doi.org/10.3923/rjmp.2011.116.126
8. Agidew MG (2022) Phytochemical analysis of some selected traditional medicinal plants in Ethiopia. Bull Natl Res Cent 46(1):87. https://doi.org/10.1186/s42269-022-00770-8
9. Velu G, Palanichamy V, Rajan AP (2018) Phytochemical and pharmacological importance of plant secondary metabolites in modern medicine in bioorganic phase in natural food: an overview. Roopan SM, Madhumitha G, Eds Cham: Springer, 135–156. https://doi.org/10.1007/978-3-319-74210-6_8.

10. Bouguellid G (2020) Antimutagenic, antigenotoxic and antiproliferative activities of Fraxinus angustifolia Vahl. leaves and stem bark extracts and their phytochemical composition. PLOS ONE 15(4):e0230690. https://doi.org/10.1371/journal.pone.0230690.
11. Swargiary A, Roy MK, Verma AK (2021) In vitro study of the antioxidant, antiproliferative, and anthelmintic properties of some medicinal plants of Kokrajhar district, India. J Parasit Dis 45(4):1123–1134. https://doi.org/10.1007/s12639-021-01410-0
12. Naseem U, Muhammad Z, Farhat Ali K, Shazeb K (2014) A review on general introduction to medicinal plants, its phytochemicals and role of heavy metal and inorganic constituents. Life Sci 11(7):520–527
13. Dave Mehta S, Upadhyay S, Rai G (2022) Importance of flavonoid as secondary metabolites in flavonoid metabolism: recent advances and applications in crop breeding. IntechOpen 2022. https://doi.org/10.5772/intechopen.107462
14. Gonçalves BMF, Cardoso DSP, Ferreira MJU (2020) Overcoming multidrug resistance: flavonoid and Terpenoid nitrogen-containing derivatives as ABC transporter modulators. Molecules 25(15):3364. https://doi.org/10.3390/molecules25153364
15. Ullah A (2020) Important flavonoids and their role as a therapeutic agent. Molecules 25(22):5243. https://doi.org/10.3390/molecules25225243
16. Kumar S, Pandey AK (2013) Chemistry and biological activities of flavonoids: an overview. Sci World J 2013:162750. https://doi.org/10.1155/2013/162750
17. Panche AN, Diwan AD, Chandra SR (2016) Flavonoids: an overview. J Nutr Sci 5:e47. https://doi.org/10.1017/jns.2016.41
18. Nix A, Paull C, Colgrave M (2017) Flavonoid profile of the cotton plant. Gossypium Hirsutum: Rev Plants 6(4):43. https://doi.org/10.3390/plants6040043
19. Tungmunnithum D, Thongboonyou A, Pholboon A, Yangsabai A (2018) Flavonoids and other phenolic compounds from medicinal plants for pharmaceutical and medical aspects: an overview. Med Basel Switz 5(3):93. https://doi.org/10.3390/medicines5030093
20. Wang L (2018) Gossypin inhibits gastric cancer growth by direct targeting of AURKA and RSK2. Phytother Res p ptr 6253. https://doi.org/10.1002/ptr.6253
21. Prabhakaran D, Rajeshkanna A, Senthamilselvi MM, Solomon S (2019) In vitro antioxidant and anti-inflammatory activities of the flower extracts of Hibiscus vitifolius L. Eur J Med Plants 1–8. https://doi.org/10.9734/ejmp/2019/v29i430160
22. Singh A (2017) Ethics in herbal medicine. Ethno leaflets 11:206–211
23. Khalaf SS, Shalaby OA, Hassan AR, El-Kherbetawy MK, Mehanna ET (2023) Acacia nilotica stem bark extract ameliorates obesity, hyperlipidemia, and insulin resistance in a rat model of high fat diet-induced obesity. J Tradit Complement Med 13(4):397–407. https://doi.org/10.1016/j.jtcme.2023.03.005
24. Chapano C (2003) Plants of the Chimanimani District National Herbarium and Botanic Garden, Zimbabwe. 32
25. Karimah A (2021) A comprehensive review on natural fibers: technological and socio-economical aspects. Polymers 13(24):4280. https://doi.org/10.3390/polym13244280
26. Kumar ChMS (2023) Solar energy: a promising renewable source for meeting energy demand in Indian agriculture applications. Sustain Energy Technol Assess 55:102905. https://doi.org/10.1016/j.seta.2022.102905
27. Revathi P (2013) Western Ghats of Tamil Nadu. J Medi Pla Res 7(28):2083–2097
28. Huang J, Chen X (2022) New function of gossypol, a natural product of cotton. J Cotton Res 5(1):28. https://doi.org/10.1186/s42397-022-00135-6
29. Tanyeli A, Eraslan E, Güler MC, Kurt N, Akaras N (2019) Gossypin Sıçanlarda Böbrek İskemi- Reperfüzyon Hasarına Karşı Korur. Kafkas Univ Vet Fak Derg 2019. https://doi.org/10.9775/kvfd.2019.22396
30. Tian X (2018) Characterization of gossypol biosynthetic pathway. Proc Natl Acad Sci 115:23. https://doi.org/10.1073/pnas.1805085115
31. A kind of preparation method of gossypin ether sizing agent. (2016) https://patents.google.com/patent/CN106120336A/en?q=(gossypin)&oq=gossypin
32. Nair H, Veerapaneni P, Sophie D, Kirma N, Perla R, Tekmal R (2009) Nanogossypin, a novel cdk2/VEGF inhibitor formulation against breast cancer. Cancer Res 69(2):3080. https://doi.org/10.1158/0008-5472.SABCS-3080
33. Bhardwaj JS (2020) Protective effects of gossypin in colchicine-induced cognitive dysfunction and oxidative damage in rats
34. Shabanzadeh E, Monajjemi M (2015) A nano-biotechnology study of gossypin-CNT as a productive drug for the treatment of diabetes. J Comput Nano 12(11):4076–4086
35. Song B (2023) Gossypin: a flavonoid with diverse pharmacological effects. Chem Biol Drug Des 101(1):131–137. https://doi.org/10.1111/cbdd.14152
36. Shrikumar S (2007) Approaches towards development and promotion of herbal drugs. Pharmacogn Rev 1(1)
37. Rao KV, Seshadri TR (1946) Constitution of gossypin—Part I. Proc Indian Acad Sci - Sect A 24(4):375. https://doi.org/10.1007/BF03171074
38. Amawi H, Ashby CR, Tiwari AK (2017) Cancer chemoprevention through dietary flavonoids: what's limiting? Chin J Cancer 36(1):50. https://doi.org/10.1186/s40880-017-0217-4
39. Awouafack MD, Tane P, Morita H (2017) Isolation and structure characterization of flavonoids. In: Flavonoids - from biosynthesis to human health. Justino GC, Ed InTech. https://doi.org/10.5772/67881
40. Safety data sheet. https://www.biosynth.com/Files/MSDS/MH/11/MSDS_MH11045_5000_EN.pdf
41. Jahangir MA (2022) Phytonutrients and technological development in formulations. J Pharm Res Sci Technol 6(1):38–66. https://doi.org/10.31531/jprst.1000159
42. Rajkumar J, Radha GV, Ganapaty S (2021) Topical drug delivery of gossypin from proniosomal gel formulations: In Vitro efficacy against human melanoma cells. Int J Appl Pharm 144–152. https://doi.org/10.22159/ijap.2021v13i1.39609
43. Nagpal D, Agarwal N, Katare D (2016) Evaluation of liposomal gossypin in animal models of epilepsy. Int J Pharm Pharm Sci 8(4)
44. Ngere JB, Ebrahimi KH, Williams R, Pires E, Walsby-Tickle J, McCullagh JSO (2023) Ion-exchange chromatography coupled to mass spectrometry in life science, environmental, and medical research. Anal Chem 95(1):152–166. https://doi.org/10.1021/acs.analchem.2c04298
45. Yang L, Cao YL, Jiang JG, Lin QS, Chen J, Zhu L (2010) Response surface optimization of ultrasound-assisted flavonoids extraction from the flower of *Citrus aurantium* L. var. amara Engl: Other Techniques. J Sep Sci 33(9):1349–1355. https://doi.org/10.1002/jssc.200900776
46. Liu Y, Wang H, Cai X (2015) Optimization of the extraction of total flavonoids from Scutellaria baicalensis Georgi using the response surface methodology. J Food Sci Technol 52(4):2336–2343. https://doi.org/10.1007/s13197-014-1275-0
47. Our report on Gossypin market with 9% CAGR, covers the following areas: market sizing, market forecast, market industry analysis (2023–2030), 2023, https://www.marketwatch.com/press-release/our-report-on-gossypin-market-with-9-cagr-covers-the-following-areas-market-sizing-market-forecast-market-industry-analysis-2023---2030-2023-04-04
48. Technological Advancements and Regional Gossypin Market Size Report 2023–2030. (2023) https://www.marketwatch.com/press-release/technological-advancements-and-regional-gossypin-market-size-report-2023-2030-2023-04-12
49. Global Gossypin Market 2023 by Manufacturers, Regions, Type and Application, Forecast To 2029. (2023) https://www.absolutereports.com/global-gossypin-market-22462505
50. Hibiscus Flower Powder Market Size, Share & Trends Analysis Report by Nature (Organic, Conventional), by Application (Food & Beverages, Pharmaceuticals, Personal Care & Cosmetics), by region, and Segment Forecasts, 2020 - 2027. (2023) https://www.grandviewresearch.com/industry-analysis/hibiscus-flower-powder-market.
51. Venkatesan T, Sorimuthu Pillai S (2012) Antidiabetic activity of gossypin, a pentahydroxyflavone glucoside, in streptozotocin-induced experimental diabetes in rats: antidiabetic property of gossypin. J Diabetes 4(1):41–46. https://doi.org/10.1111/j.1753-0407.2011.00145.x
52. Saravanamuttu S, Sudarsanam D (2012) Antidiabetic plants and their active ingredients: a review. 3(10):3639–3650
53. Mada SR, Metukuri MR, Burugula L, Reddanna P, Krishna DR (2009) Antiinflammatory and antinociceptive activities of gossypin and procumbentin - cyclooxygenase-2 (COX-2) inhibition studies: antiinflammatory activity of gossypin and procumbentin. Phytother Res 23(6):878–884. https://doi.org/10.1002/ptr.2727
54. Ferrándiz ML, Alcaraz MJ (1991) Anti-inflammatory activity and inhibition of arachidonic acid metabolism by flavonoids. Agents Actions 32(3–4):283–288. https://doi.org/10.1007/BF01980887

55. Ferrándiz ML, Nair AG, Alcaraz MJ (1990) Inhibition of sheep platelet arachidonate metabolism by flavonoids from Spanish and Indian medicinal herbs. Pharm 45(3):206–208
56. Babu BH, Jayram HN, Nair MG, Ajaikumar KB, Padikkala J (2003) Free radical scavenging, antitumor and anticarcinogenic activity of gossypin. J Exp Clin Cancer Res CR 22(4):581–589
57. Shi L (2012) Gossypin Induces G2/M arrest in human malignant glioma U251 cells by the activation of Chk1/Cdc25C pathway. Cell Mol Neurobiol 32(2):289–296. https://doi.org/10.1007/s10571-011-9760-8
58. Kunnumakkara AB (2007) Gossypin, a pentahydroxy glucosyl flavone, inhibits the transforming growth factor beta-activated kinase-1-mediated NF-κB activation pathway, leading to potentiation of apoptosis, suppression of invasion, and abrogation of osteoclastogenesis. Blood 109(12):5112–5121. https://doi.org/10.1182/blood-2007-01-067256
59. Viswanathan S, Thirugnana Sambantham P, Reddy K, Kameswaran L (1984) Gossypin-induced analgesia in mice. Eur J Pharmacol 98(2):289–291. https://doi.org/10.1016/0014-2999(84)90604-6
60. Ganapaty S, Chandrashekhar VM, Narsu ML (2010) Evaluation of anti-allergic activity of gossypin and suramin in mast cell-mediated allergy model. Indian J Biochem Biophys 47:2010
61. Lee JH, Kim YS, Lee CK, Lee HK, Han SS (1999) Antiviral activity of some flavonoids on herpes simplex viruses. Korean J Pharmaco 30(1):34–39
62. Zhang Y (2022) Cotton flower metabolites inhibit SARS-CoV-2 main protease. FEBS Open Bio 12(10):1886–1895. https://doi.org/10.1002/2211-5463.13477
63. Ganapaty S, Chandrashekhar V, Chitme H, Ml N (2007) Free radical scavenging activity of gossypin and nevadensin: an in-vitro evaluation. Indian J Pharmacol 39(6):281. https://doi.org/10.4103/0253-7613.39147
64. Chandrashekhar V, Ganapaty S, Ramkishan A, Narsu Ml (2013) Neuroprotective activity of gossypin from Hibiscus vitifolius against global cerebral ischemia model in rats. Indian J Pharmacol 45(6):575. https://doi.org/10.4103/0253-7613.121367
65. Rasilingam D, Duraisamy S, Subramanian R (2008) Anticonvulsant activity of bioflavonoid gossypin. Bangladesh J Pharmacol 4(1):51–54. https://doi.org/10.3329/bjp.v4i1.1081
66. Lu N, Li Y, Qin H, Zhang X, Sun C (2008) Gossypin up-regulates LDL receptor through activation of ERK pathway: a signaling mechanism for the hypocholesterolemic effect. J Agric Food Chem 56(23):11526–11532. https://doi.org/10.1021/jf802607x
67. Cinar I (2022) In vivo and in vitro cardioprotective effect of gossypin against isoproterenol-induced myocardial infarction injury. Cardiovasc Toxicol 22(1):52–62. https://doi.org/10.1007/s12012-021-09698-3
68. Cheng G (2022) Cardioprotective effect of gossypin against myocardial ischemic/reperfusion in rats via alteration of oxidative stress, inflammation and gut microbiota. J Inflamm Res 15:1637–1651. https://doi.org/10.2147/JIR.S348883
69. Gautam P, Flora SJS (2010) Oral supplementation of gossypin during lead exposure protects alteration in heme synthesis pathway and brain oxidative stress in rats. Nutrition 26(5):563–570. https://doi.org/10.1016/j.nut.2009.06.008
70. Kim KY (2008) (−)-epigallocatechin gallate inhibits the pacemaker activity of interstitial cells of cajal of mouse small intestine. Korean J Physiol Pharmacol Off J Korean 12(3):111–115. https://doi.org/10.4196/kjpp.2008.12.3.111
71. Viswanathan S, Thirugnana Sambantham P, Bapna JS, Kameswaran L (1984) Flavonoid-induced delay in the small intestinal transit: possible mechanism of action. Arch Int Pharmacodyn Ther 270(1):151–157
72. Alam MA, Al-Jenoobi FI, Al-mohizea AM (2012) Everted gut sac model as a tool in pharmaceutical research: limitations and applications. J Pharm Pharmacol 64(3):326–336. https://doi.org/10.1111/j.2042-7158.2011.01391.x
73. Vijayaraghavan R, Sugendran K, Pant SC, Husain K, Malhotra RC (1991) Dermal intoxication of mice with bis(2-chloroethyl)sulphide and the protective effect of flavonoids. Toxicology 69(1):35–42. https://doi.org/10.1016/0300-483X(91)90151-P
74. Vijayaraghavan R, Gautam A, Sharma M, Satish H, Pant S, Ganesan K (2008) Comparative evaluation of some flavonoids and tocopherol acetate against the systemic toxicity induced by sulphur mustard. Indian J Pharmacol 40(3):114. https://doi.org/10.4103/0253-7613.42304
75. Gautam A, Vijayaraghavan R (2007) Prophylactic effect of gossypin against percutaneously administered sulfur mustard. Biomed Environ Sci 20:250–259
76. Yoon I, Lee KH, Cho J (2004) Gossypin protects primary cultured rat cortical cells from oxidative stress- and β-amyloid-Induced toxicity. Arch Pharm Res 27(4):454–459. https://doi.org/10.1007/BF02980089
77. Añón MT, Ubeda A, Alcaraz MJ (1992) Protective effects of phenolic compounds on $CCl_4$-induced toxicity in isolated rat hepatocytes. Z Für Naturforschung C 47(3–4):275–279. https://doi.org/10.1515/znc-1992-3-417
78. Kardeş S (2016) Neuroprotective effect of Gossypin on glutamate-induced excitotoxic neuronal death in SH-SY5Y cell line. Toxicol Lett 258:S286. https://doi.org/10.1016/j.toxlet.2016.06.1997
79. Bhaskaran S (2013) Gossypin as a novel selective dual inhibitor of v-raf murine sarcoma viral oncogene homolog B1 and cyclin-dependent kinase 4 for melanoma. Mol Cancer Ther 12(4):361–372. https://doi.org/10.1158/1535-7163.MCT-12-0965
80. Thamizhiniyan V, Vijayaraghavan K, Subramanian SP (2012) Gossypin, a flavonol glucoside protects pancreatic beta-cells from glucotoxicity in streptozotocin-induced experimental diabetes in rats. Biomed Prev Nutr 2(4):239–245. https://doi.org/10.1016/j.bionut.2012.07.002
81. Yildiz K, Turalioglu MF, Tahiroglu V, Boy F, Yigit S (2021) Gossypin'in Fare Mekano-Biyoregülatör Modeli Deneysel Femur Kırıklarında Kırık İyileşmesi Üzerine Etkileri. Kafkas Univ Vet Fak Derg 2021. https://doi.org/10.9775/kvfd.2021.25516.
82. Marc Winnefeld Sabine Hagemann Jörn Söhle Elke Grönniger Torsten Schläger Katrin Schmidt, Use of gossypetin and/or gossypin against skin aging. (2016) https://patents.google.com/patent/WO2016034400A1/en?q=(gossypin)&oq=gossypin
83. The preparation method of the super thin fabric face of a kind of water and oil repellant. (2016) https://patents.google.com/patent/CN102633249B/en?q=(gossypin)&oq=gossypin
84. Method for rapidly preparing carbon microspheres by using cotton cellulose. (2014) https://patents.google.com/patent/CN102633249B/en?q=(GOssypin)&oq=GOssypin
85. A kind of medical dressing hydrogel compound fabric and its preparation method and application. (2018) https://patents.google.com/patent/CN105228658B/en?q=(gossypin)&oq=gossypin


## Publisher's Note