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Chemical constituents and pharmacological activities of *Gossypium herbaceum* and *Gossypium hirsutum* - A review

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Abstract: The phytochemical investigations of *Gossypium herbaceum* showed that it contained carbohydrates, flavonoids, tannins, steroids, terpenoids, saponins, resins, phenols and proteins, while, *Gossypium hirsutum* contained alkaloids, phenolic compounds, terpenoids, tannins, saponins flavonoids, cardiac glycosides and protein. The pharmacological investigations revealed that they possessed anti-diabetic, hypolipidemic, antioxidant, anticancer, antidepressant, antiepileptic, memory enhancement, wound healing, nephroprotective, hepatoprotective, antimicrobial, anthelmintic, antiprotozoal, insecticidal, diuretic, gastric ulcer healing and wide range of effects on reproductive systems. This review discussed the chemical constituents and pharmacological effects of *Gossypium herbaceum* and *Gossypium hirsutum*.

Keywords: chemical constituents, pharmacology, therapeutic, medicinal plants, *Gossypium herbaceum*, *Gossypium hirsutum*

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I. INTRODUCTION:

Since the dawn of civilization, man utilized plants for their medicinal and edible value. Recent reviews showed that plants produce many secondary metabolites which are bio-synthetically derived from primary metabolites and constitute an important source of many drugs[1-40]. The phytochemical investigations of *Gossypium herbaceum* showed that it contained carbohydrates, flavonoids, tannins, steroids, terpenoids, saponins, resins, phenols and proteins, while, *Gossypium hirsutum* contained alkaloids, phenolic compounds, terpenoids, tannins, saponins flavonoids, cardiac glycosides and protein. The pharmacological investigations revealed that they possessed anti-diabetic, hypolipidemic,

antioxidant, anticancer, antidepressant, antiepileptic, memory enhancement, wound healing, nephroprotective, hepatoprotective, antimicrobial, anthelmintic, antiprotozoal, insecticidal, diuretic, gastric ulcer healing and wide range of effects on reproductive systems. This review was designed to highlight the chemical constituents and pharmacological effects of *Gossypium herbaceum* and *Gossypium hirsutum*.

Plant profile:

Synonyms:

Gossypium herbaceum:

Gossypium albescens Raf., *Gossypium album* Buch.-Ham., *Gossypium amblospermum* Raf., *Gossypium arboreum var. perrieri* (Hochr.) B. L. Rob., *Gossypium aureum* Raf., *Gossypium bicolor* Raf., *Gossypium chinense* Fisch. & Otto ex Steud., *Gossypium cinereum* Raf., *Gossypium convexum* Raf., *Gossypium croceum* Buch.-Ham, *Gossypium decurrens* Raf, *Gossypium divaricatum* Raf., *Gossypium eglandulosum* Cav.,*Gossypium elatum* Salisb., *Gossypium frutescens* (Delile) Roberty, *Gossypium fuscum* Raf., *Gossypium herbaceum var. acerifolium* (Guill. & Perr.) A. Chev., *Gossypium herbaceum var. frutescens* Delile, *Gossypium herbaceum var. herbaceum, Gossypium herbaceum var. perrieri* Hochr., *Gossypium hirsutum var. micranthum* (Cav.) Roberty, *Gossypium hirsutum subsp. paniculatum* (Blanco) Mauer, *Gossypium hirsutum var. paniculatum* (Blanco) Roberty, *Gossypium leoninum Medik., Gossypium macedonicum* Murray, *Gossypium macrospermum* Raf., *Gossypium micranthum* Cav., *Gossypium molle* Mauri ex Ten., *Gossypium paniculatum* Blanco, *Gossypium perrieri* (Hochr.) Prokh., *Gossypium punctatum var. acerifolium* Guill. *& Perr, Gossypium purpureum* Raf., *Gossypium siamense* Ten. ,*Gossypium simpsonii G.Watt, Gossypium strictum Medik., Gossypium tricuspidatum* Lam. , *Gossypium vitifolium* Roxb. , *Hibiscus nangking* Kuntze, *Xylon hirsutum* Medik., *Xylon indicum* Medik and *Xylon leoninum* Medik[41].

Gossypium hirsutum

Gossypium hirsutum subsp. *latifolium* (Murray) Roberty, *Gossypium hirsutum* var. *marie-galante* (G. Watt) J. B. Hutch., *Gossypium hirsutum* var. *punctatum* (Schumach.) Roberty, *Gossypium jamaicense* Macfad., *Gossypium lanceolatum* Tod., *Gossypium mexicanum* Tod., *Gossypium morrillii* O. F. Cook & J. Hubb., *Gossypium palmeri* G. Watt, *Gossypium punctatum* Schumach., *Gossypium purpurascens* Poir., *Gossypium religiosum* L., *Gossypium schottii* G. Watt, *Gossypium taitense* Parl. and *Gossypium tridens* O. F. Cook & J. Hubb[42].

Taxonomic classification:

Kingdom: Plantae, **Division:** Magnoliophyta, **Class :** magnoliopsida, **Order:** malvales, **Family:** malvaceae, **Genus:** *Gossypium*, **Species:** *Gossypium herbaceum* and *Gossypium hirsutum* [43-44].

Common names:

Gossypium herbaceum:

Chinese: cao mian**; English:** Arabian cotton, Levant cotton, Maltese cotton, short-staple cotton, Syrian cotton; **French**: cotonnier d'Asie, cotonnier herbacé; **German**: gewöhnliche Baumwolle, krautiger Baumwollstrauch; **Hindi**: Kapas; **Japanese**: shiro-bana-wata; **Portuguese**: algodoeiro-asiático; **Spanish:** algodonero, algodonero herbáceo; **Swedish:** indisk bomull[41].

***Gossypium hirsutum*:**

Arabic: cotton; **Chinese**: lu di mian; **English**: American cotton, American upland cotton, Bourbon cotton, cotton, upland cotton; **French**: coton velu, cotonnier américain; **German**: amerikanische Baumwolle, uplandbaumwolle; **Hindi**: Kaarpaasii; **Portuguese**: algodoeiro-americano; **Spanish**: algodonero Americano; **Swedish**: texasbomull[42].

Distribution:

Gossypium herbaceum:

Gossypium herbaceum originated in southern Africa but was first domesticated in Arabia, from where cultivated forms spread westward to Africa and eastward to India. At present it is cultivated in Africa, Asia, and in the new World**.** It is found in Africa: (Swaziland, Botswana, Namibia, South Africa), Asia (China, Pakistan, Nepal, Tajikistan, Turkmenistan, Uzbekistan, Afghanistan, India, Iraq, Iran) and wide areas in Europe Central America and the Caribbean[45-46].

Gossypium hirsutum

*Gossypium hirsutum*native was orginated in the Northern and Southern America. *Gossypium hirsutum* was became the main cotton of commerce and was widely cultivated throughout the warmer parts of the world included tropical north and central America, tropical Africa, Pakistan, India, Russia, China, Turkey, Iraq, Iran, Egypt and Sudan[47-48].

Description:

Gossypium herbaceum:

Perennial or annual shrub or subshrub up to 3 m tall, with few branches; stem thick and rigid, stem and branches hairy or glabrous. Leaves spirally arranged; stipules small, linear, caducous; petiole 2–3.5 cm long; blade 3–7-lobed, cut less than halfway, 2–6 cm × 2–7 cm, base cordate, lobes ovate to rounded, only slightly constricted at the base, upper surface glabrescent, lower surface stellate hairy. Flowers solitary, usually on sympodial branches; pedicel 7–30 mm long, not articulated, glandless; epicalyx segments (bracteoles) 3, flaring widely from the flower and the fruit, rounded or broadly triangular, cordate at base, margin with 5–13 triangular teeth, persistent; calyx 5–10 mm long; corolla yellow or

white with a dark centre, petals 5, 2.5-5 cm long; stamens numerous, , filaments short, anthers 1-celled; pistil with 3-5-celled ovary and one short style, stigma entire. Fruit a rounded capsule 2-3.5 cm long, beaked, surface smooth or very shallowly dented, with few oil glands. Seed ovoid, with a dense covering of long, pure white, woolly hairs, strongly attached to the seed[49].

***Gossypium hirsutum*:**

Annual herb, 0.6-1.5 m tall. Branchlets sparsely villous. Stipules ovate-falcate, 5-8 mm, caducous; petiole 3-14 cm, pilose; leaf blade broadly ovate, 3(-5)-lobed, 5-12 cm in diam., lobes broadly triangular to ovate-orbicular, base broad, central lobe usually 1/2 as long as leaf blade, abaxially sparsely villous, adaxially nearly glabrous, scabrously hairy on veins, base cordate or cordate-truncate, apex acuminate. Flowers solitary, axillary. Pedicel usually slightly shorter than petiole. Epicalyx lobes 3, free, to 4 × 2.5 cm (including teeth), hirsuta and ciliate with long hairs, base cordate, with 1 gland, 7-9-toothed near apex, teeth 3 or 4 × as long as wide. Calyx cup-shaped, 5-lobed, lobes triangular, ciliate. Corolla white or yellowish, fading to reddish or purple, funnelform; petals 4-5.5 × 3.5-4.5 cm. Staminal column 1-2 cm; filaments lax, upper ones longer. Capsule 3- or 4-celled, ovoid, 3.5-5 cm, apex beaked. Seeds free, ovoid, with white wool and gray-white moderately persistent short fuzz. Fl. summer-autumn[48,50].

Parts used medicinally:

Seeds, leaves, flowers, root and root bark[51-52].

Traditional uses:

Gossypium herbaceum:

Gossypium spp was an earliest plants that were cultivated by man and it has been used for over 4,000 years. It is primarily cultivated for fiber used in the textile industry. The genus *Gossypium* spp. includes many species distributed throughout the world, but only four species are grown for cotton fiber: *Gossypium hirsutum* L., *Gossypium barbadense* L., *Gossypium arboretum* L., and *Gossypium herbaceum* L. The most economically important cotton species is *Gossypium hirsutum*, which is grown to produce 90% of the world's cotton[53-54]. Medicinally, cotton seeds were used as pain reliever, as a nervine tonic in treating of headache and migraine, the decoctions of the seed were given in intermittent fever. The seeds and flowers in the form of poultice were applied to burns. Seeds were also used in epilepsy and as an antidote to snake poison. The juice of the leaves and the decoctions of the seed were used in dysentery [55-57].

Leaves, root and seeds of *Gossypium herbaceum* were used to augment labour, in retention of placenta and as emmenagogues. In Senegal a root maceration was given to

new-born babies and sickly or rachitic children, to strengthen them. In Somalia a root decoction was used as an abortifacient and the juice of the heated unripe fruit was dropped into the ear against earache. In Ethiopia the root was chewed in case of a snake bite and the powdered fruit was applied on the head for the treatment of fungal infections. In Namibia the powdered root bark was applied as a haemostatic. In Botswana root preparations were used for the treatment of heart palpitations. In Mozambique root decoctions were used as a tonic and to control vomiting, and the infusion of the root against lack of appetite. The stem juice was used in otitis [49].

***Gossypium hirsutum*:**

Seed and roots were used in nasal polyps, uterine fibroids and other types of cancer. Mucilaginous tea of fresh or roasted seeds were used for bronchitis, diarrhea, dysentry, and hemorrhage. Flowers were used as diuretic, emollient and in hypochondriasis. Leaves steeped in vinegar were applied to the forehead for headache. It was used by early American slaves for abortion. Root decocotion was used for asthma, diarrhea, and dysentery. Root bark, devoid of tannin, astringent, antihemorrhoidal; used as an emmenagogue, hemostat, lactagogue, oxytocic, parturient, and vasoconstrictor. Gossypol was used in China as a male contraceptive [58-59]. Root decoction was used for the treatment of asthma, diarrhea, and dysentery. Root bark was used to stimulate secretion of breast milk. Seeds were used for the treatment of swelling and ulceration of female organs, and urinary diseases. Extract of seed coat was used for the treatment of fungal infections. Women use the plant in menstrual disorders and to decrease the symptoms of menopause and to enhance labor[60-61]. In Benin, a decoction of the leaves of *Gossypium hirsutum* and those of *Flueggea virosa* (Roxb. ex Willd.) Voigt was taken for the treatment of intestinal colic, constipation, low blood pressure and asthenia. The powdered seed or a seed decoction was taken against convulsions with fever. In East Africa the root was chewed or a root decoction drunk against stomach-ache[62].

Physicochemical characteristics:

Physicochemical analysis of *Gossypium herbaceum* flower revealed that: foreign matter % < 2, loss on drying at 105^0C % 11.37, total ash content % 10.38, acid insoluble ash % 0.48, water soluble extractive % 16.20, alcohol soluble extractive % 6.75, volatile oil % Nil[56].

The physicochemical parameters of cotton seeds were: loss on drying 5% w/w, total ash 4% w/w, acid insoluble ash 0.08 % w/w, sulphated ash 5% w/w, water extractable value 9% w/w, PH value 4.5[23] While, the Physicochemical parameters of the root were: PH value 7.2, loss on drying, 6.47, ash value (%w/w) 5.2, acid insoluble ash (%w/w) 0.02, water soluble extract (%w/w) 5.6 and alcohol soluble extract (%w/w) 8.80[64].

Chemical constituents:

Gossypium herbaceum:

The preliminary phytochemical investigations of the flower showed the presence of carbohydrates, flavonoids, tannins, steroids, terpenoids, saponins, resins, phenols and proteins [56].

The phytochemical analysis of cotton seed showed that they contained steroids, flavonoids, protein, amino acids, sugars and saponins[63]. While, *Gossypium herbaceum* root contained starch, tannin, phenols, saponin and carbohydrates[64].

The principle pigment of cotton seed was gossypol. Gossypol was a phenolic compound that was first isolated in 1899. The name was derived from the plant genus scientific name (*Gossypium*) combined with the ending (ol) from phenol. Gossypol molecular weight: 518.55 Dalton, has a yellow pigment, crystalline, insoluble in water and hexane, soluble in acetone, chloroform, ether, and methyl ethyl ketone and was partly soluble in crude vegetable oils. The chemical formula was $C_{30}H_{30}O_8$, and the chemical structural formula was 2,2-bis(8-formyl-1,6,7-trihydroxy-5-isopropyl-3-methylnaphthalene. Gossypol was a mixture of two enantiomers, (−) and (+) gossypol. The *Gossypium* species produced both enantiomers in varying proportions. Total gossypol production was influenced by several factors, including weather conditions and cotton species. Gossypol production was positively correlated with the rainfall rate and negatively correlated with temperature. On the other hand, two gossypol forms have been observed, free and bound, gossypol concentrations range from 0.02 to 6.64%. Cotton seeds may contain concentrations greater than 14,000 mg/kg of total gossypol and 7,000 mg/kg of free gossypol[53,65-67].

Other pigments present in the seed were included gossypupurin, gossyfulvin, gossycaerulin, carotenoids and flavones. Sitosterol and ergostoerol, lactic acid, choline, betaine and sulphydryl compounds were identified in the unsaponifiable fraction of Indian cotton seed oil[68].

Total flavonoid content in the extract was found to be 410 ± 0.74 mg quercetin equivalents/g of dry material. Total phenolic content in *Gossypium herbaceum* was found to be 5.86 ± 0.75 mg gallic acid equivalents/g of dry material[69].

The mineral constituents of the cotton seed were: phosphorus 1.03-1.33, calcium 0.24-0.04, iron 0.02-0.03, potassium 0.94-1.07, sodium 0.05-0.14, magnesium 0.44-0.56 manganese 0.03-0.04, aluminium 0.01- 0.06, silica 0.12-0.39, sulphur 0.17-0.28 and chlorine 0.92-0.04%. Traces of copper, boron, zinc, nickel, strontium and barium were also recorded. Cotton seed was rich in vitamins of the B-complex, thiamine 3.2, riboflavin, 2.3, nicotinic acid 16, pantothenic acid 11, pyridoxine 0.91, biotin 0.29, inositol 3.400 and folic acid 3.8 ug/g dry weight. Vitamins A, D, and E are also present[11,28]. *Gossypium herbaceum* leaves contained many heavy metals included Zn: 4.84 ± 0.03, Fe: 0.37 ± 0.02, Cd 0.12 ± 0.02 and Pb 0.75 ± 0.03 mg/kg, they were below the limits of WHO (15.0, 100.0, 0.3 and 10.0 mg/kg, respectively)[70].

Gossypium hirsutum

Phytochemicals analysis of differential solvent extracts of the leaves of *Gossypium hirsutum* showed that they contained alkaloids, phenolic compounds, terpenoids, tannins, saponins flavonoids, cardiac glycosides and protein[71].

Quantitive analysis revealed that *Gossypium hirsutum* contained alkaloids 12.20± 0.28%, saponins 2.63±0.04 %, flavonoids 11.90±0.4 %, tannins 2.73 mg/100g, total phenol 1.62±0.00 mg/100g**,** moisture content 15.04 ± 0.01%, ash 18.72 ± 0.13%, crude fat 6.57 ± 0.04%, crude fiber 8.31 ± 0.04%, crude protein 2.70 ± 0.01%, carbohydrate 48.66 ± 0.31%, phosphorus 29.05 ± 0.01mg/100g, calcium 31.69 ± 0.01mg/100g, magnesium 8.32 ± 0.00mg/100g, potassium 38.61 ± 0.00mg/100g and sodium 3.37 ± 0.00mg/100g[72].

Gossypol content of the seeds and leaves of *Gossypium hirsitium* dried sample was 847.00 and 297.00 mg/100g respectiviley[73].

The total phenolic determination, showed that the seeds of *Gossypium hirsitium* contained 11mg/g GAE phenolic compounds[74].

A diglycosylated flavonol (3-glucoside-7-rhamnoside of 3,5,7,4′-tetrahydroxy -8-methoxyflavone) was isolated from immature flower buds of *Gossypium hirsutum*[75]. Kaempferol, quercetin, and hyperoside flavonoids were also extracted from the ethanol extract of the flowers of *Gossypium hirsutum* [76].

A condensed tannin having a molecular weight of 4850 was isolated from methanolic extract of *Gossypium hirsutum* by column chromatography on Sephadex G-25 (3.4% of the dried flower bud)[77].

Terpenoid products, including monoterpenes, sesquiterpenes, and terpenoid aldehydes were identified in the leaf foliage of *Gossypium hirsutum*[78]. The triterpenoid aldehydes, gossypol, 6-methoxygossypol and 6,6′-dimethoxygossypol, and the sesquiterpenoid aldehydes, hemigossypol and methoxyhemigossypol, were isolated from 1-week-old roots of *Gossypium hirsutum* and *G. barbadense*[79]. Two new sulfated cadinene-type sesquiterpene glycosides, 13-hydroxy-7-O- (60-O- sulfate-b-D- glucopyranosyl)-desoxyhemigossypol and 13,15-dihydroxy -7-O- (60-O -sulfate-b-D-glucopyranosyl)-desoxyhemigossypol were isolated from whole *Gossypium hirsutum*[80].

The total sesquiterpenes of the essential oil extract of *Gossypium hirsitium* reached 26.12%. The sesquiterpenes, α-bergamotene, caryophyllene, bisabolene, farnesene, humulene and copanene were some of the sesquiterpenes commonly associated with cotton[81] .

Glucose-containing polysaccharides were isolated from the culture medium of *Gossypium hirsutum*[82]. Cotton honeydew extract was composed of a unique combination of oligosaccharides, included fructose, glucose, inositol, melezitose, saccharose, trehalose and trehalulose[83].

Pharmacological effects:

Effects on male and female fertility:

Gossypol acts as an inhibitor for several dehydrogenase enzymes and has proapoptotic properties, affecting both spermatogenesis and sperm motility[84].

Gossypol has been investigated for use as a male contraceptive in a number of experimental studies. Gossypol (10mg/kg bw /day) caused degeneration of spermatocytes in hamsters, (20mg/kg bw /day) caused degeneration of spermatocytes in rats, (25mg/kg bw /day) decreased spermatogenesis, Sertoli cell, and caused seminiferous tubules damage in rats. (10mg/kg bw /day) caused tubular degeneration, reduced testosterone level, and involutions of ventral prostate and seminal vesicles (5, 10 and 20mg/kg bw /day) decreased sperm count and motility, increased abnormal sperm count, and reduced serum levels of testosterone, LH, and FSH in rats, (16.4mg/kg bw/day) reduced sperm production and motility and increased proportion of sperm midpiece abnormalities in bulls, (8mg/kg bw /day) caused primary and secondary sperm abnormalities and increased number of sperm with proximal droplets in bulls[85-90].

Some authors mentioned that the main target organ of gossypol toxicity following repeated exposure to lower doses in rats and humans is the testis with reduced sperm motility, inhibited spermatogenesis and depressed sperm counts[91].

It was used as male contraceptive by Chinese, It was noted that men consuming cottonseed oil in their diet showed unusually high infertility rates. Oral administration of gossypol in large scale trials resulted in severe oligozoospermia (< 1 million/ml) at 90% of participants. In 20% of men, this effect was irreversible. Because some cases showed severe hypokalemia, WHO recommend the discontinuation of further investigations on gossypol[84].

The male contraceptive effects of gossypol were mediated via inhibition of release and utilization of ATP by the sperm cells, reduction of cellular and microtubular β-tubular content in spermatocytes and spermatids, inhibitition of calcium influx, and Mg-ATPase and Ca-Mg-ATPase activity in spermatozoid plasmatic membranes. Gossypol produced ultrastructural alterations in the nuclear membrane, endoplasmic reticulum, and mitochondria, decreased cellular oxidase activity and damaged sperms DNA, reduced nuclear expression of androgen receptors in Leydig cells, Sertoli cells, and myoid cells from in rats. It also decreased testosterone, LH and FSH serum levels [88,92-96].

Gossypol also affected female fertility, (5mg/kg bw/day) caused longer diestrus in female rats, (25mg/kg bw/day) decreased the levels of estradiol-17β in female rats, (20mg/kg bw/day) caused irregular and longer estrous cycles, prolonged time for mating, decreased pregnancy rate, and reduced number of viable embryos in rats, (5 g of free gossypol/animal/day) reduced number of ovarian follicles >5mm in heifers[97-100].

Using of 20 mg/day of racemic gossypol for 2-3 months followed by a maintenance dose of 40 mg/week for 4-5 months in women with endometriosis, uterine myomas and functional uterine bleeding, resulted in amenomania and atrophy of the endometrium.

Examination of uterine biopsies showed a local cytotoxic effect on the uterus together with a systemic effect on the ovarian function[101-103].

Furthermore, gossypol affected male and female gametogenesis and caused embryo toxicities[104].

Anticancer effect:

Gossypol showed antiproliferative effect on many cancer cells *in vitro*: adrenal, prostate and mammary carcinomas, gliomas, endometriosis and uterine myoma[105].

Six hours incubation of HEp-2 cells with gossypol at concentrations of 50 μM and 75 μM resulted in the increase of apoptosis rate by 26 and 23%, respectively[106].

The action of gossypol on a number of drug-sensitive and multidrug-resistant cell lines, in particular MCF-7 WT and MCF-7 ADR cells, was studied and compared to the effects of rhodamine 123. P nuclear magnetic resonance spectra of cells exposed to low concentrations of gossypol exhibited decreased levels of ATP, markedly increased levels of pyridine nucleotides, and decreased levels of glyceryl-phosphocholine[107].

The cytotoxicity of the (-)- and (+)-isomers and the quinone metabolite gossypolone were compared using two human melanoma cell lines (SK-mel-19 and SK-mel-28) with a similar growth rate, one melanotic (melanin content of 69 pg/cell) and one amelanotic (melanin content of 10 pg/cell). Results from two viability assays (MTT and flow cytometry) showed that the cytotoxicity of racemic gossypol was identical for both cell lines (IC_{50} = 22 microM). Gossypolone at equimolar concentrations was inactive in the amelanotic cell line and as potent as racemic gossypol in the melanotic cell line. (-)-Gossypol was significantly more active in both cell lines compared with the (+)-isomer[108].

The pro-differentiated effects, of gossypol on the classic human myeloid leukemia HL-60 cell line was studied *in vitro* using morphological changes, nitroblue tetrazolium (NBT) reduction, surface markers, cell-cycle analysis and Western blot analysis. When HL-60 cells were incubated with low concentrations of gossypol (2-5 μM) for 48hr, a prominent G0/G1 arrest was observed[109].

Two human breast carcinoma cell lines (MCF-7, MCF-7 Adr) and rat esophageal cancer cell line (RE-B2T) were used to evaluate the antiproliferative potential of gossypol - containing milk (GP-Milk), which was collected from Brown Swiss dairy cows treated daily with federally allowable 450 ppm of gossypol for 6 days. Treatment of the cultured cancer cells with gossypol- milk for 24 h significantly inhibited the rates of ^{3}H-thymidine incorporation during the ensuing 3-h period in all three tumorigenic cell lines. The inhibitory effects of gossypol- milk occurred in a dose-dependent manner in all cases, but the calculated ED_{50} varied with cell lines. ED_{50} for gossypol- milk was estimated at 10% for wild-type MCF-7 human breast cancer cells, 15% for multidrug-resistant MCF-7 Adr human breast cancer cells and 50% for RE-B2T rat esophageal carcinoma cells[110].

The efficacy of oral gossypol as a treatment for adrenal cancer was studied in humans. Twenty-one patients with metastatic adrenal cancer received oral gossypol at doses of 30-70 mg/day. Eighteen patients completed at least 6 weeks of gossypol treatment. 13 patients had disease progression. Gossypol was generally well tolerated; the only recorded side effect was abdominal ileus that resolved when the drug was temporarily withheld and restarted at a lower dose[111].

The interaction of gossypol with cultured murine erythroleukemia cells (MELC) was studied *in vitro*. gossypol possessed cytocidal effect, it inhibited the growth greater than 90%[112].

The effects of gossypol were examined in several cell lines including hamster V79 lung fibroblasts, WB-344 rat liver oval cells, human osteosarcoma cells and LC540 rat Leydig cells. Gossypol had little cytotoxic effects on these cell lines except at high concentrations. Gossypol inhibited gap junctional intercellular communication in some but not all of the cell lines. This selectivity might be the basis for the sensitivity of certain tissues or organs to gossypol. Leydig cell, a target organ system for toxicity, was sensitive to gossypol. Modulation of gap junctional functions might play a significant role in both pharmacological and toxicological effects of gossypol[113].

The cytotoxic effect of the BH3-mimetic AT101 [(-)-gossypol] on MPNST cells was studied *in vitro* with the identification of key regulators of AT101-induced MPNST cell death. AT101 caused caspase-independent, non-apoptotic MPNST cell death, accompanied by autophagy and was mediated through HIF-1α induced expression of the atypical BH3-only protein BNIP3[114].

Gossypol inhibited proliferation and induced apoptosis in human uterine leiomyoma and myometrial cells. The mechanisms of action involved reducing the protein level of Bcl-2 and the activity of Src and ERα.[115]

The (-) enantiomer of gossypol possessed higher affinity for Bcl-2 and Bcl-XL. Aberrant overexpression of antiapoptotic members of the Bcl-2 protein family, including Bcl-2 and Bcl-XL, contributed to malignant transformation and subsequent resistance to traditional chemotherapeutics. Thus, these proteins represent attractive targets for novel anticancer agents[116-117].

The ability of the (-) enantiomer of gossypol, to overcome the apoptosis resistance conferred by Bcl-2 or Bcl-XL overexpression was studied in Jurkat T leukemia cells. (-) -Gossypol potently induced cell death in Jurkat cells overexpressing Bcl-2 (IC_{50}, 18.1 F 2.6 μmol/l) or Bcl-XL (IC_{50}, 22.9 F 3.7 μmol/l). Vector-transfected control cells were also potently killed by (-)-gossypol (IC_{50}, 7.0 F 2.7 μmol/l). By contrast, the chemotherapy drug etoposide only induced efficient killing of vector-transfected cells (IC_{50}, 9.6 F 2.3 μmol/l). Furthermore, (-)-gossypol was more efficient than etoposide at inducing caspase-3 activation and phosphatidylserine externalization in the setting of Bcl-2 or Bcl-XL overexpression. (-)-Gossypol-induced apoptosis was associated with Bak activation and release of cytochrome c

from mitochondria, suggesting a mitochondrial mediated apoptotic mechanism. In addition, (-)-gossypol treatment of isolated mitochondria purified from Bcl-2- overexpressing cells also resulted in cytochrome c release, indicating a possible direct action on Bcl-2 in the mitochondrial outer membrane. The results indicated that (-)-gossypol was able to overcome apoptosis resistance by specifically targeting the activity of antiapoptotic Bcl-2 family members[117].

Two sulfated cadinene-type sesquiterpene glycosides isolated from whole *Gossypium hirsutum,* were screened for their toxicity on Jurkat cells. Both compounds inhibited cellular proliferation with IC_{50} values of 8.1 and 4.2 mg, respectively[80].

Effect on memory and learning:

The protective effect of *Gossypium herbaceam* extracts (GHE) on learning and memory impairment associated with aging were examined *in vivo* using Morris water maze and step through task. Furthermore, the antioxidant activity and neuroprotective effect of GHE was investigated histochemically and biochemically. The results showed that oral administration of GHE at the doses of 35, 70, and 140 mg/kg improved the learning and memory impairment in aged rats. It also afforded a beneficial action on eradication of free radicals without influence on the activity of glutathione peroxidase and superoxide dismutase. GHE treatment enhanced the expression levels of nerve growth factor. The proliferation of neural progenitor cells was elevated in hippocampus after the treatment[118].

The acetylcholinesterase (AChE) inhibition and antioxidant activity of a standardized extract from the flowers of the *Gossypium herbaceam* (GHE) as well as the protective effects to PC12 cells against cytotoxicity induced by tertiary butyl hydroperoxide (tBHP) were investigated using *in vitro* assays. The antioxidant activities were assessed by measuring their capabilities for scavenging 1,1-diphenyl-2-picylhydrazyl (DPPH) and 2-2'-azinobis- (3-ethylbenzothiazoline -6- sulfonic acid) (ABTS) free radical as well as in inhibiting lipid peroxidation. The results revealed that GHE exhibited activitiy against AChE and possessed efficient free radical scavenging activity, which may be helpful in preventing or alleviating patients suffering from Alzheimer's disease[119].

Antiepileptic effect:

The antiepileptic activity of aqueous extract of *Gossypium herbaceum* (AEGH) at 10, 30, and 100 mg/Kg, po was evaluated against the convulsions induced in mice by maximum electroshock (MES), pentylenetetrazole (PTZ) and isoniazid (INH). In MES method, aqueous extract of *Gossypium herbaceum* inhibited convulsions significantly potent than diazepam. In PTZ method, aqueous extract of *Gossypium herbaceum* inhibited convulsions potent than phenobarbitone sodium. In INH method, aqueous extract of *Gossypium herbaceum* delayed the onset of convulsions with a potency less than diazepam[120].

The anticonvulsant activity of gossypin was investigated on seizures induced by pentelentetrazole, strychnine and maximal electroshock convulsive methods in mice. Gossypin (10 and 20 mg/kg) significantly reduced the duration of convulsion in tonic seizure induced by pentelenetetrazole (95 mg/kg, ip). In a dose of 20 mg/kg po, it significantly reduced the tonic extensor convulsion induced by strychnine and maximum electroshock-induced convulsions[121].

Antidepressant effect:

Aqueous extract of detoxified *Gossypium herbaceum* seeds showed antidepressant-like effect due to activation of adenyl cyclase-cAMP pathway in signal transduction system. Aqueous extract of detoxified *Gossypium herbaceum* seeds 0.01, 0.03, 0.10, 0.30 mg/ml was incubated directly with the synaptic membrane extracted from the cerebral cortex in rats, and adenylyl cyclase activity was detected by radio-immunoassay. The results showed that the antidepressant and anxiolytic effects of the aqueous extract of detoxified *Gossypium herbaceum* seeds were caused by activation of AC-cAMP pathway in signal transduction system, thus protecting neurons from the lesion[1222-123].

Antioxidant effects:

The antioxidant activity of hydroalcoholic leaves extract (70: 30) of *Gossypium herbaceum* was evaluated by determining reducing power, total flavonoids and total phenolic contents. The DPPH radical scavenging activity of the extract was increased with the increasing concentration. The IC_{50} values for DPPH assay of *Gossypium herbaceum* and ascorbic acid were found to be 44.69µg/ml and 13.80µg/ml respectively. The reducing power of the extract was concentration dependent. Total flavonoid content in the extract was 410 ± 0.74 mg quercetin equivalents/g of dry material. Total phenolic content in *Gossypium herbaceum* was 5.86 ± 0.75 mg gallic acid equivalents/g of dry material[69].

Gossypol antioxidant effect was documented by *in vitro* and *in vivo* methods. Gossypol inhibited rat liver microsomal peroxidation caused by incubation with ferric/ascorbate[84]. It also protected supercoiled plasmid DNA from damage in the presence of Fe_3/ ascorbate, in a dose-dependent manner[125].

Modification of phenolic hydroxyl groups on gossypol significantly decreases the chemical antioxidative abilities of free radical scavenging activity, reducing power assay, DNA damage prevention, and demonstrating that the hydroxyl groups were critical to antioxidation[126].

The aqueous and ethanolic extract of *Gossypium herbasceum* seeds were analyzed for reducing power ability using the 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay. The results revealed that *Gossypium herbasceum* showed percentage antioxidant activity (AA%) of 26.62, 27.86, 31.09, 32.78 and 40.53 for the aqueous extract (10, 25, 50, 125 and 250µg/ml) of the seeds and 53, 80.34, 85.83, 91.60 and 92.81 for the

ethanolic extract (10, 25, 50, 125 and 250µg/ml) of the seeds respectively. *Gossypium herbasceum* also showed high reductive potential of 0.90nm at the same concentration compared with gallic acid whose reductive potential was 0.93nm[(74)].

Anti-diabetic and hypolipidemic effects:

The inhibitory effect of aqueous extract of different parts (bark, leaf, and flower) of cotton plant (*Gossypium herbaceum)* on key enzymes linked with type 2 diabetes and oxidative stress was studied in rat pancreas *in vitro*. The ability of the extract to inhibit the activity of α-amylase and α-glucosidase as well as activities of pro-oxidant Fe^{2+}-induced lipid peroxidation was determined spectrophotometrically. The results revealed that the extracts were able to inhibit the activity of α-amylase and α-glucosidase in rat's pancreas in a dose dependent manner (0–88.8 mg/ml). Incubation of pancreas tissue homogenate in the presence of Fe^{2+} caused a significant increase (233.3%) in the malondialdehyde (MDA) content of pancreas homogenate, nevertheless, the introduction of the aqueous extract inhibited MDA production, dose dependently (0–33.33 mg/ml) and also exhibited further antioxidant properties represented by their high radical scavenging and Fe^{2+} chelating abilities[(127)].

Anti-diabetic and hypolipidemic effects of seed of *Gossypium herbaceum* and its aqueous and ethanol extracts were investigated in alloxan-induced diabetic rabbits. *Gossypium herbaceum* powder, its aqueous (GHA) and ethanol (GHE) extract significantly ($P<0.05$) reduced glucose, cholesterol, triglyceride and urea in a dose dependent order (200-300 mg/kg of body weight) in normal rabbits. *Gossypium herbaceum* and GHE ameliorated completely the alloxan effect on serum levels of glucose, cholesterol, triglyceride, creatinine and urea in alloxan-induced diabetic rabbits. Histopathological examination confirmed the protective effect of *Gossypium herbaceum*, GHA and GHE against alloxan-induced destruction of β-cells of pancreas in diabetic rabbits[(128)].

The hypoglycemic and hypolipidemic effects of ethyl ether and ethanol extracts of *Gossypium herbaceum* (200mg/kg) leaves were evaluated in alloxan induced diabetes in rat. The extracts showed significant ($P<0.01$) antihyperglycemic and hypolipidemic activity as compared to diabetic control. The extracts possessed beneficial effects on blood glucose level in alloxan model. It also reduced the elevated biochemical parameters such as triglycerides, low density lipoprotein, very low density lipoprotein, total cholesterol and increased the reduced level of high density lipoprotein[(129)] .

Wound and hair effects:

The healing activity of *Gossypium herbaceum* leaves methanolic extract has been proved by using excision, incision and dead space wound models in rats. In incision and excision models, a significant decrease in period of epithelization and wound contraction was observed in all the treatment groups when compared to control. In the incision wound

model, a significant increase in the breaking strength was observed. Granulation tissue formation significantly increased in all treated animals compare to control[130].

The wound healing activity of ethanol and ethyl ether fractions of leaves of *Gossypium herbaceum* was investigated by dexamethasone delayed wound healing model in rats. *Gossypium herbaceum* decreased glucose level against dexamethasone. In excision wound model wound contraction area was increased, the epithelization period and scar area were decreased with significantly increase in percentage of wound healing in *Gossypium herbaceum* treated groups. In incision mode, a combination of extract plus dexamethasone significantly increases the breaking strength. Hydroxyproline content significantly increased in the treated groups compare to dexamethasone group[131].

Cotton honeydew extract is composed of a unique combination of oligosaccharides, including fructose, glucose, inositol, melezitose, saccharose, trehalose and trehalulose. Studies have shown that these oligosaccharides exhibited a protective effect. Furthermore, the effect of these oligosaccharides was studied in normal and damaged human hair. Both clinical and scanning electron microscopy (SEM) studies were performed. Standardized human hair samples were used to determine the effect of a rinse-off mask with 1% cotton honeydew extract on the ultrastructure of hair. In addition, hair samples were submitted to different aggressions, following various experimental protocols. SEM showed that, without extra aggression, the cuticle scales appeared to lie more smoothly in the hair in cotton honeydew extract-treated samples than in untreated samples. The extract-treated hair samples were also less prone to chipping. In a clinical study, 15 volunteers had half of their hair treated with a formula with 1% honeydew extract and the other half was left untreated as a control. Pictures and visual evaluation of the hair showed that the honeydew extract formula left the hair with a smoothness and this result was confirmed by SEM. In addition, mRNA study on epidermal cells confirmed the stimulating effect of honeydew extract on keratin synthesis[83].

Protective effect:

The nephroprotective activity of alcoholic and aqueous root extracts of *Gossypium herbaceum* was investigated in gentamicin induced nephrotoxicity in rats. Both alcoholic and aqueous extract at the dose of 250 and 500 mg/kg bw showed significant nephroprotective activity as evident by increase in urine output, with a decrease in the elevated serum creatinine and serum urea. The protective effect was further confirmed by histopathological study[132].

The protective effect of *Gossipium hirsutum* extracts was studied in acute experimental hepatic injury in rats. *Gossipium hirsutum* extracts significantly decrease the serum transaminase activities ($P < 0.01$), increased the SOD activities ($P < 0.01$) and decreased MDA content[133].

Antimicrobial effect:

Gossypium herbaceum and *Gossypium hirsutum* showed activity against *B. cerus* and *Salmonella thyphimurium*. Free flavonoid fraction of seeds of *Gossypium herbaceum* and *Gossypium hirsutum* showed activity against *B. cerus, S. epidermidis, Trichoderma viride, Salmonella typhimurium, E. coli* and *Trichoderma viride*[134].

Gossypol possessed pronounced antibiotic activity towards aerobic sporeformers and lactobacilli, and was also antagonistic to some of the more oxidative yeasts[135].

The antimicrobial effect of gossypol was tested against *Edwardsiella ictaluri*. Concentrations of racemic gossypol, (+)-gossypol and (-)-gossypol of 1.5 µg/ ml or higher significantly reduced the number of bacterial colonies compared with that of the control. The growth of *Edwardsiella ictaluri* was completely inhibited on agar plates supplemented with 3 µg/ ml, regardless of the forms of gossypol. The inhibitory effect of (+)-gossypol was higher than that of (-)-gossypol or gossypol-acetic acid [136].

Leaves extracts of *Gossypium hirsutum* showed antibacterial activity against clinically important bacteria like *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Shigella dysenteriae*. Ethanolic extract possessed more antibacterial activity than aqueous extract, *Shigella dysenteriae* was the more sensitive microorganism (13mm) and *Pseudomonas aeruginosa*, was the least sensitive (6mm). The minimum inhibitory concentration was 0.25 (% w/v) against all the tested bacteria[137].

The antimicrobial activity of *Gossypium hirsutum* oils was investigated against *Escherichia coli, Trichophyton rubrum* and *Candida albicans* by agar well diffusion method. *Gossypium hirsutum* oils possessed antibacterial and antifungal activity with a diameter of inhibition of 12.33, 10, 10.16 mm against *Escherichia coli, Trichophyton rubrum* and *Candida albicans* respectively at a concentration of 1 mg/ ml [138].

Low antibiotic activity was found in hexane extract, high activity in methanolic extract and residue, and no activity in acetone and water extracts of *Gossypium hirsutum* buds. A condensed tannin isolated from methanolic extract was the major antibiotic component[77].

Basic proteins isolated from seeds of cotton (*Gossypium hirsutum*) were found to have selective growth inhibitory activity *in vitro* against the filamentous fungi *Botrytis cinerea*, *Alternaria brassicicola*, *Chalara elegans* and *Fusarium oxysporum*. These proteins differ, however, from numerous other seed antifungal proteins in being neither substrates nor inhibitors of signal transduction elements such as wheat germ Ca^{2+}-dependent protein kinase (CDPK), rat liver cyclic AMP-dependent protein kinase (PKA) catalytic subunit (cAK), rat brain Ca^{2+}- and phospholipid-dependent protein kinase (PKC) and chicken gizzard calmodulin-dependent myosin light chain kinase (MLCK)[139].

Gossypol possessed antiviral properties against enveloped viruses, including HIV-1, HSV-2, influenza, and parainfluenza[140-144]. Incubation of HTLV-III B strain of human

immunodeficiency virus with gossypol, showed that gossypol prevented recovery of viable viruses when subsequently incubated with H9-T cells[145].

Racemic mixture and both enantiomers of gossypol inhibited the replication of human immunodeficiency virus-type 1 (HIV-l). Variety analogs of gossypol showed more activity against immunodeficiency virus-type 1 (HIV-l)[140].

The antiviral effect of water extracts of *Gossypium hirsutum* leaves was investigated for their inhibitory activities on the yellow fever virus in the tissue cell culture using Vero cells. The extracts showed antiviral activities against yellow fever virus. It inhibited yellow fever viruses at MICs of 0.079mg/ml[146].

Anthelmintic antiprotozoal and insecticidal effects:

The N-hexane, ethyl ether and ethanol extracts of leaves of *Gossypium herbaceum* were investigated for anthelmintic activity using earthworms (*Pheretima posthuma*). Various concentrations (10, 20, 40, 60, 80 and100 mg/ml) of plant extracts were tested in a bioassay. The ethyl ether and ethanol extracts exhibited significant anthelmintic activity at highest concentration (60, 80 and 100 mg/ml) compared to standard drug (Albendazole 10 mg/ml). The result showed that ethyl ether extract possessed potent vermicidal activity and found to be effective as an anthelmintic compared to ethanolic extract[147].

The anti-leishmanial activity of methanolic extracts of *Gossypium hirsutum* was studied on *Leishmania major* promastigotes by colorimetric assay in comparison to a trivalent antimony compound (tartar emetic). The plant extracts and tartar emetic inhibited the growth of promastigote stage of *Leishmania major* after 72 hours of incubation. Tartar emetic as positive control gave a 50% inhibitory concentration (IC_{50}) of 4.7µg/ml, while the IC_{50} values of *Gossypium hirsutum* was 3.6 µg/ml[148-149].

The lethal effect of *Gossypium hirsutum* extract on *Toxoplasma gondii* tachyzoites were studied *in vitro*. Tachyzoites of *Toxoplasma gondii* RH strain were treated with concentrations of 10, 50, 100, and 200 mg/ml of *Gossypium hirsutum* extracts within 10, 30, and 45 min. The lowest mortality rate of *Gossypium hirsutum extract* at concentration of 10 mg/ml was 4.63±2.1[150].

Gossypol was effective in the immobilization of *Tryponosoma cruzi* , *Tryponosoma brucei* and *Plasmodium falciparum*[151-154].

Gossypol and its enantiomers were showed a potent *in vitro* anti-amoebic effect against several strains of *Entamoeba histolytica*[155-157].

Anti-amoebic effect of gossypol was studied in golden hamsters with experimental hepatic amoebic abscess. Hamsters with experimental amoebic hepatic abscess were fed acetic acid gossypol (0–45 mg/kg) or metronidazole (30 or 45 mg/ kg) for 5 or 10 days. The experimental amoebic hepatic abscess size and the *in vitro* cell density reached by trophozoite cultures from the experimental amoebic hepatic abscesses were scored. Gossypol and metronidazole reduced the experimental amoebic hepatic abscess. The

smallest effect of gossypol was obtained with 5-45 mg/kg (23-31% score reduction) administered for 5 days, whereas the most effective treatment was 30 mg/kg gossypol for 10 days (90% score reduction)[158].

The plant leaves were extracted by different solvents and the extracts were tested to control of different larval stages of mosquito species, *Ae. aegypti* and *An. stephensi*. LC_{50} values of water, ethanol, ethyl acetate and hexane extracts for *Ae. aegypti* were 211.73±21.49, 241.64±19.92, 358.07±32.43, 401.03±36.19 and for 4th instar of *An. stephensi* were 232.56±26.00, 298.54±21.78, 366.50±30.59, 387.19±31.82, respectively. The water extract displayed lowest LC_{50} value followed by ethanol, ethyl acetate and hexane. Owing to the comparatively better activity of water extract, its efficacy was further evaluated for mosquito larvicidal activity, which exhibited LC_{50} values of 133.95±12.79, 167.65±11.34 against 2nd and 3rd instars of *Ae. aegypti* and 145.48±11.76, 188.10±12.92 against 2nd and 3rd instars of *An. stephensi*, respectively. Crude protein was tested against 2nd, 3rd and 4th instars of *Ae. aegypti* and *An. stephensi*. It revealed further decrease in LC_{50} values (105.72±25.84, 138.23±23.18, 126.19±25.65) and (134.04±04, 137.88±17.59, 154.25±16.98) for 2nd, 3rd and 4th instars of *Ae. aegypti* and *An. stephensi,* respectively[71].

Diuretic effect:

The diuretic activity of ethyl acetate and alcohol extract of *Gossypium herbaceum* leaves (100 and 200 mg/kg bw) was investigated in male wistar albino rats. The total urine volumes of the both extracts (200mg/kg) treated rats were elevated nearly two folds compared with the control. Excretion of sodium, potassium and chloride ions were increased significantly compared with control group. The diuretic effect was comparable with that of the standard drug frusemide. However, alcoholic extract showed more significant diuretic activity compared with the ethyl acetate extract. The increase of sodium and potassium in the urine of the group treated with both extracts was dose dependent[46].

Gastric ulcer healing effect:

The aqueous and ethanolic extracts of flowers of *Gossypium herbaceum* increased healing of gastric ulcer and possessed potential antiulcer activity[159].

Effect on milk production:

Cottonseed feeding enhances the milk production in buffaloes significantly ($P<0.0l$) in comparison to commercial concentrate mixture fed control group animals[160-161].

Toxicity:

The ingestion of gossypol present in cottonseed and its products (cakes and meal) may promote clinical poisoning. The free gossypol content in whole cotton seeds varies among cotton varieties. Cottonseed contained sufficiently high gossypol concentrations to

produce acute poisoning. However, gossypol was accumulated and toxicity can occur following an ingestion period of one to three months[162-164].

Gossypol absorption was negatively proportional to the amount of iron in the diet, dietary supplementation with ferrous sulfate inactivated free gossypol. The absorbed gossypol accumulated in the liver and kidneys and mainly excreted through bile in feces as glucuronides and sulfate conjugates[165-168].

Monogastric animals such as birds, fish and rodents were more susceptible to gossypol toxicity than ruminants. However, gossypol toxicity was recorded in chicks, pigs, dogs, sheep and goats[103,165,169-176].

Ruminants such as cattle and sheep can tolerate higher levels of free gossypol because gossypol bind to proteins in the rumen. Adult cattle can tolerate much larger amounts of free gossypol but toxic cases were reported with levels of 800ppm fed over a long period of time. Young calves and lambs were quite susceptible to gossypol. Gossypol primarily affected heart and liver. The reproductive tract, abomasum, and kidney were also affected. General signs of acute toxicity were similar in all animal species and include respiratory distress, impaired body weight gain, anorexia, weakness, apathy, and death after several days. However, gossypol toxicity were manifested as two types of clinical syndromes particularly in young animals. The first was a syndrome of sudden death (resembling a heart attack) which was frequently reported in calves and lambs. The other syndrome characterised by chronic labored breathing, which resembles pneumonia. Due to heart failure, the lungs fill up with fluid and breathing becomes very difficult. Animals will be depressed, go off feed, may have a nasal discharge, may have red urine and may have a thin but pot-bellied appearance in contrast to the animals that died suddenly[177-178].

The postmortem signs included pulmonary edema, yellowish liquid in the chest and peritoneal cavities, gastroenteritis, centrilobular liver necrosis, and hypertrophic cardiac fiber degeneration[179-181].

II. CONCLUSION:

The current review discussed the chemical constituents, pharmacological effects and therapeutic importance of *Gossypium herbaceum* and *Gossypium hirsutum*.

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