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Chemical constituents, pharmacological effects and therapeutic importance of *Hibiscus rosa-sinensis*- A review

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Abstract: The phytochemical analysis showed that *Hibiscus rosa-sinensis* contained tannins, anthraquinones, quinines, phenols, flavanoides, alkaloids, terpenoids, saponins, cardiac glycosides, protein, free amino acids, carbohydrates, reducing sugars, mucilage, essential oils and steroids. The previous pharmacological studies revealed that *Hibiscus rosa-sinensis* possessed reproductive, antidiabetic, fibrinolytic, hypolipidemic, antioxidant, antiinflammatory, antipyretic, analgesic, immuno-modulatory, anticonvulsant, antidepressant, memory enhancement, cytotoxic, antimicrobial, antiparasitic, dermatological, anti-haemolytic, urinary, hepatoprotective, neuroprotective, antitussive and many other effects. The current review will discuss the chemical constituents, pharmacological effects and therapeutic importance of *Hibiscus rosa-sinensis.*

Keywords: *Hibiscus rosa-sinensis*, chemical constituents, pharmacology, therapeutic, side effects.

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I. INTRODUCTION:

Herbal medicine is the oldest form of healthcare known to mankind. Herbs had been used by all cultures throughout history. As a result of accumulated experience from the past generations, today, all the world's cultures have an extensive knowledge of herbal medicine. Plants are a valuable source of a wide range of secondary metabolites, which are used as pharmaceuticals, agrochemicals, flavours, fragrances, colours, biopesticides and food additives[1-40]. The current review will discuss the chemical constituents, pharmacological effects and therapeutic importance of *Hibiscus rosa-sinensis.*

Plant profile:

Synonyms:

Hibiscus arnottii Griff. ex Mast.; *Hibiscus boryanus* DC.; *Hibiscus cooperi* auct.; *Hibiscus festalis* Salisb., *Hibiscus liliiflorus* Griff. ex Mast., *Hibiscus rosiflorus* Stokes and *Hibiscus storckii* Seem[41].

Taxonomic classification:

Kingdom: Plantae, **Subkingdom**: Tracheobionta**, Superdivision**: Spermatophyta**, Division**: Magnoliophyta**, Class**: Magnoliopsida**, Subclass**: Dilleniidae**, Order**: Malvales, **Family**: Malvaceae**, Genus**: *Hibiscus*, **Species**: *Hibiscus rosa-sinensis*[42].

Common names:

Arabic: Bent EL-Kunsil, Ward El-Jemal, Khatmah Siniyah**,** Hab misk Seni**,** Pooq Seni; **Chinese:** Zhu jin, Da hong hua, Fo sang, Fu sang**; English:** China-rose, Chinese hibiscus, Hawaiian hibiscus, hibiscus, rose-of-China; **French:** Hibiscus de Chine, Hibiscus rose de Chine, Rose de Chine; **German:** chinesischer Roseneibisch; **Italian:** Rosa della Cina; **Japanese**: Aka-bana, Fusou, Haibisukasu; **Portuguese**: rosa-da-China; **Spanish**: clavel japonés; **Swedish**: hibiscus[43].

Distribution:

The probable origin of the plant was tropical Asia, It was cultivation in China, Japan and the Pacific islands for an equally long time, it was generally thought that it was originated in South China. The plant with deep-red flowers is believed to have an Asian origin, hence the name *rosa-sinensis* meaning 'rose of China. Now it is widely cultivated[43-46].

Traditional uses:

In medicine, the red flowered variety was preferred**.** Roots and leaves, were anodyne and emmenagogue. They were used to regulate menstruation and stimulate blood circulation. Leaves were also used as abortifacient and to stimulate expulsion of placenta after childbirth. Flower were used for regulation of menstrual cycle, for liver disorders, high blood pressure as antitussive, in stomach pain, for eye problems, as abortifacient and as an aphrodisiac. Young leaves and flowers were used in headache. Decoction of leaves, root

and fruits were helpful in treatments of arthritis, boils and coughs. Fruits were employed externally in cases of sprains, wounds and ulcers[47-50].

The leaves of *Hibiscus rosa-sinensis* were used for the treatment of dysentery and diarrhea, to promote draining of abscesses and as analgesic in the traditional medicine of Cook Islands, Haiti, Japan and Mexico[51]. Flowers of the plant were used in diabetes, epilepsy, bronchial catarrh and leprosy[52-53]. The flowers have been reported in the ancient Indian medicinal literature with beneficial effects in heart diseases. They were refrigerant, emollient, demulcent, aphrodisiac and emmenagogue. Petals were used to stimulate thicker hair growth and to prevent premature graying, hair loss and scalp disorders. It considered as a natural emollient hair conditioner and was used in hair washes, treatments and vinegar rinses for the hair[54-55].

Parts used: Whole plant[9].

Physicochemical characteristics:

The physicochemical parameters of the root extract: loss on drying 0.53%; ash values: total ash 7.75%, acid insoluble ash 0.75% and water soluble ash 6.32%); extractive values (chloroform soluble extractive 2.80%, water soluble extractive 5.30%, carbinol soluble extractive 15.60%, ethanol soluble extractive 2.60% and petroleum ether soluble extractive 1.45%) and swelling Index 2.5%[56].

Chemical constituents:

The preliminary phytochemical analysis showed that *Hibiscus rosa-sinensis* contained tannins, anthraquinones, quinines, phenols, flavanoides, alkaloids, terpenoids, saponins, cardiac glycosides, protein, free amino acids, carbohydrates, reducing sugars, mucilage, essential oils and steroids[57-61].

Hibiscus rosa-sinensis contained cyclopropanoids, methyl sterculate, methyl-2-hydroxy sterculate, 2-hydroxysterculate, malvalate and beta-sitosterol. The major anthocyanin in the flower was cyanidin 3-sophoroside[62].

Quantitative phytochemical evaluation of the flowers of *Hibiscus rosa-sinensis* revealed that the amount of flavonoids was 0.171 mg/g, total phenolics 0.092 mg/g, tannins 0.073 mg/g, carbohydrates 0.356 mg/g, protein 0.247 mg/g, thiamine 0.072 mg/g, niacin 0.075 mg/g, ascorbic acid 0.0339 mg/g, riboflavin 0.087 mg/g, calcium 0.0127%, phosphorus 0.4113% and iron 0.771%[63].

The flower extract of *Hibiscus rosa-sinensis* (Red) contained 0.678±0.14% phenols, 0.51±0.16 % alkaloids and 7.5±0.20 % tannins. While , the flower extract of *Hibiscus rosa-sinensis* (White) contained 0.680±0.11% phenols, 0.50±0.18 % alkaloids and 8.9±0.21 % tannins, and the flower extract of *Hibiscus rosa-sinensis* (Yellow) contained 0.678±0.16% phenols, 0.48±0.16 % alkaloids and 8.5±0.20% tannins[64].

Total phenolic contents of leaves and flowers of *Hibiscus rosa-sinensis* were: 301 ± 21 and 735±46 mg gallic acid equivalent /100g respectively, ascorbic acid equivalent antioxidant capacity (AEAC) of the leaves and flowers were 96 ± 35 and 640 ± 56 mg ascorbic acid /100g respectively, total anthocyanin content (TAC) in the flowers was 284 ± 17 mg cyanidin-3-glucoside equivalent/100g, and ferric-reducing power (FRP) of flowers was 4.0 ± 0.3 mg gallic acid equivalent /100g[65].

The flowers contained four types of flavonoids, rutin, quercetin, kaempferol and myricetin, their contents in methanol extract were 4104.0, 7.6, 361.9 and 50.7 µg/g respectively[66].

The flowers also contained substantial quantities of proanthocyanidins and anthocyanins[67]. Many compounds were isolated from the flowers included cyclopeptide alkaloids, vitamins, thiamine, riboflavin, niacin and ascorbic acid[68-69]. Crushed red and magenta flower varities yield dark-purplish dye, anthocyanin pigment and cyandin diglucoside, while many flavanoids and cyanidin compounds (quercetin-3-diglucoside, quercetin 3,7-diglucoside, kaempferol-3-xylosyglucoside, cyanidin- 3,5 -diglucoside and cyanidin-3-sophoroside-5-gIucoside) were isolated from other varieties [70-71].

Fresh flowers of *Hibiscus rosa-sinensis* gave 0.30 - 0.50 v/w % essential oils. Many constituents were identified in the essential oils included: 1 - iodoundecane: 50.568%, neopentane: 7.641%, 2, 2, 4-trimethyl 3-pentanone: 1.556%, 1,2-benzenedicarboxylicacid isodecyl octyl ester: 11.056%, 2-cyclopentylethanol: 2.404%, 2-propeonic acid, 1-4 butanediyl ester: 1.543%, 2-propenamide: 1.543%, 1-tetrazol-2-ylethanone: 3.993%, 4-trifluoroacetoxyoctane: 1.480% and amylnitrite: 3.993%[72].

Methanol and ethanol extract of *Hibiscus rosa-sinensis* showed total phenolics 61.45 ± 3.23 and 59.31 ± 4.31 mg/100g as gallic acid equivalent, total flavonoids 53.28 ± 1.93 and 32.25±1.21 mg/100g as catechine equivalent, respectively[73].

The extracted mucilage was slightly soluble in water and a dispersion of it yielded a brown, slimy solution and it was practically insoluble in ethanol, acetone and chloroform. A 1% w/v suspension of Hibiscus mucilage in water gave a pH of 6.5. Mucilage of *Hibiscus rosa-sinensis* contained L-rhamnose, D-galactose, D-galactouronic acid, and D-glucuronic acid[74-76].

The metals in decoction of *Hibiscus rosa- sinensis* leaves were determined by atomic absorption spectrophotometer, they were included: Sodium 129.6 - 344.2, Potassium 612.9 - 787.2, Calcium 748.3 -

907.5, Magnesium 574.8 - 877.9, Iron 1.16 - 2.53, Zinc 1.32 - 1.92, Cobalt 1.25 - 1.68, Manganese 0.147 - 0.188, Chromium 0.142 - 0.164, Nickel 0.244 - 0.496, Copper 0.107 - 0.129, Lead 0.087 - 0.122, Cadmium 0.058 - 0.064, Barium 1.67 - 2.45 and Aluminum 0.299 - 0.472 mg/100g[77]. 8-Nonynoic and 9-decynoic acids and their methyl esters were isolated from stem bark [78]. Carotene and taraxeryl acetate and p-sitosterol were isolated from leaves and stem bark of the plant[79].

Pharmacological effects:

Reproductive effects:

The benzene chloroform and alcoholic extracts of the flowers of *Hibiscus rosa sinesis* decreased the spermatogenic elements of testis, and epididymal sperm count, when administered (ip) at two different dose levels (125 and 250 mg/kg bw) to adult male albino mice for 20 days. High content of testicular cholesterol may be due to lowered androgen synthesis[80].

The effect of ethanol, chloroform, ethyl acetate extract of *Hibiscus rosa sinunsis* was studied on spermatogenesis and sperm parameters on mice. Administration (Sc) of 125mg/kg bw of ethanol, chloroform and ethyl acetate extract for three consequence days caused marked to significant decrease in testis weight and sperm count and sperm viability[81].

The effects of oral administration of aqueous and alcoholic extracts of flowers of *Hibiscus rosa-sinensis* (250 mg/kg bw/day, for 30 days) on the reproductive organs of male rats were studied. The results indicated that the weights of the testis, epididymis, ventral prostate, and seminal vesicle of the treated animals were not significantly different from those of the controls. The testis and epididymis of the rats also showed normal histological features, irrespective of treatment. No apparent toxicity of the extracts was discernible[82].

The benzene chloroform and alcoholic extracts of the flowers of *Hibiscus rosa-sinensis* (125 and 250 mg/kg ip) in mice for 20 days decreased the spermatogenic elements of testis and epididymal sperm count. It also markedly increased the content of testicular cholesterol which may be occurred due to lowered androgen synthesis. The increase in the weight of accessory reproductive organs indicated the androgenicity of the plant extract[80].

The effect of orally administered aqueous crude extract of *Hibiscus rosa-sinensis* (500 mg/kg bw) on reproductive organ was studied in mice. The treatment caused reduction in the weight of testis, epididymis and sperm density significantly. Serum testosterone level was declined, the fall in density of sperms and that of testosterone level were correlated to one another. Histologically, testis in mice treated with the plant extract showed alteration in the seminiferous tubules included decrease in thickness and density of germinal epithelium and hypertrophy in majority of cells, the lumen showed negligible presence of sperms in the treated animal as compared to control[83].

The effect of *Hibiscus rosa-sinensis* on the estrous cycle and reproductive organs was studied in female albino rats. The benzene extract of the flowers disrupted the estrous cycle. Treatment for 30 days resulted in a significant ($P<0.05$) reduction in the weight of the ovaries, uterus, and pituitary gland. Histologically, ovarian follicular atresia and uterine atrophy were observed. Treatment resulted in degranulated gonadotrophs in the pituitary, the effect was dose-dependent[84].

The benzene extract of *Hibiscus rosa-sinensis* flowers administered intraperitoneally at the dose levels of 125 and 250 mg/kg bw to adult female mice, resulted in an irregular estrous cycle with prolonged estrus and metestrus. An increase in the atretic follicles and the absence of corpora lutea indicated the antiovulatory effect of the extract. The extract also showed estrogenic activity in immature mice by early opening of the vagina, premature cornification of the vaginal epithelium and an increase in uterine weight[85].

Ethanolic extracts (50%), as well the benzene extracts, of *Hibiscus rosa-sinensis* reduced significantly the glycogen contents in the uterus of adult rat, dose dependently. Benzene extract seemed more potent. These effects were due to antiestrogenic nature of the extracts[86].

The postcoital antifertility properties of benzene hot extracts of *Hibiscus rosa-sinensis* flowers, leaves, and stem barks, were investigated in female rats. Only extracts from the flowers of the plant were 100% prevented pregnancy. The flowers collected during the winter showed the greatest potency, followed by those collected in the spring, rainy season, and summer, in decreasing order[87].

Benzene extract of *Hibiscus rosa-sinensis* flowers, administered during day 1-4 of gestation, exerted anti-implantation effect without affecting the tubal transport of zygote. On day 4, normal number of blastocyst was present in the uterus, but they did not implant. However, hyper-permeability of the endometrial capillaries which is the earliest known response of a receptive endometrium to any kind of deciduogenic stimulus was inhibited by the extract. Ovarian structure exhibited signs of luteolysis. Inadequate progestational development of the endometrium due to interference with the conditioning of the uterus with progesterone during prenidatory phase of pregnancy was suggested as the plausible cause of the extract-induced implantation failure[88].

The antifertility and estrogenic activity of ethanolic extract of the roots of *Hibiscus rosa-sinensis* was investigated. A strong anti-implantation (inhibition 100%) and uterotropic activity was observed at the dose level of 400 mg/kg bw. Histological findings gave further documentation to the results[89].

The benzene extract of Hibiscus rosa-senensis flowers was administered at four different dose levels (250-1000 mg/kg bw/day) from day 1-4 postcoitus in mice. Anti-implantation response and associated changes in the uterine chemical composition were studied. With an increase in the dosage of the extract, the percentage of implantation failure increased. At the dose level of 1 gm/kg bw, the extract led to failure of implantation in 93% of the mice. The effect was accompanied by adversely altered uterine weight, its protein content and alkaline and acid phosphatase activity. The effect of the extract on uterine uptake of progesterone was studied in bilaterally ovariectomized mice treated with or without estrogen. The extract exerted neither inhibitory nor stimulatory on uterine progesterone uptake in untreated castrated mice but the estrogen-induced increase in the uptake level was significantly inhibited by the extract[90].

The antiimplantation activity of water extract of leaves of *Hibiscus rosa-sinensis* was investigated in mice. Pregnant female mice were administered with extract (100 mg/kg bw) from days 1 to 6 of pregnancy. No implantation sites were observed in day 15 of pregnancy. Biochemical and biophysical alterations were observed in the endometrium in treated animals, especially on day 5, at 4:40 a.m., the day of implantation. A sharp increase in superoxide anion radical and a sharp fall in superoxide dismutase (SOD) activity were caused by the extract, the extract also exhibited antiestrogenic activity, as judged by increase in uterine weight[91].

Oral administration of the benzene extract of *Hibiscus rosa-sinensis* flowers at a dose level of 1 gm/kg bw/day from day 5-8 of gestation caused termination of pregnancy in about 92% of female mice. The effect was associated with a significant fall in peripheral level of progesterone and increase in uterine acid phosphatase activity, as measured on day 10. The ovary exhibited signs of luteolysis, and the corpus luteal delta 5-3 beta -hydroxysteroid dehydrogenase activity decreased markedly. The interceptive effect of the extract was prevented completely by exogenous progesterone (1mg/ mouse/ day) or chorionic gonadotropin (1 IU/ mouse/ day) and partially (62.5%) by exogenous prolactin (500 micrograms/mouse/day). The extract caused resorption of the fetuses accompanied by reduction in weight of the ovaries[92].

The effect of aqueous extract of *Hibiscus rosa-sinensis* flowers was investigated in maternal-fetal outcome in pregnant rats with diabetes. The non-diabetic treated group showed decreased high density lipoprotein cholesterol, increased atherogenic index (AI) and coronary artery risk index (CRI), and increased preimplantation loss rate compared to the non-diabetic group. Although treatment with *Hibiscus rosa-sinensis* showed deleterious effects on cardiac and reproductive functions, the diabetic treated group showed increased maternal and fetal weights, reduced AI and CRI, and reduced preimplantation loss rate compared to the untreated diabetic group[93].

The effect of aqueous extract of *Hibiscus rosa-sinensis* flowers (100 mg/kg from day 0 to 7 of pregnancy, 200 mg/kg from day 8 to 14 and 400 mg/kg from day 15 to 20) was investigated on biochemical parameters and oxidative stress in diabetic and non-diabetic pregnant rats. After treatment with *Hibiscus rosa-sinensis* extract, non-diabetic and diabetic rats showed no glycemic changes. The treatment with *Hibiscus rosa-sinensis* in diabetic group was able to decrease the triglycerides and ALT levels compared to diabetic non-treated animals[94].

Antidiabetic and hypolipidemic effects:

The antidiabetic effect of ethyl acetate fraction of *Hibiscus rosa-sinensis* petals (EHRS) was evaluated in experimental diabetes at a dose of 25 mg/kg bw and compared with metformin. The elevated levels of serum glucose (398.56 ± 35.78) and glycated haemoglobin (12.89 ± 1.89) in diabetic rats were significantly decreased (156.89 ± 14.45 and 6.12 ± 0.49, respectively) by (EHRS) administration. Hepatotoxicity marker enzyme levels in serum were normalized, the glycogen content was restored by regulating the activities of glycogen metabolizing enzymes. It significantly modulated the expressions of marker genes involved in glucose homeostasis signalling pathway. Histopathological analysis of liver and pancreas supported the biochemical findings[95].

The anti-diabetic effects of aqueous ethanolic extract of *Hibiscus rosa-sinensis* was investigated in streptozotocin-induced diabetic rats. Oral administration of *Hibiscus rosa-sinensis* (500 mg/kg) aqueous extract to diabetic rats for 4 weeks significantly reduced blood glucose, urea, uric acid and creatinine but increased the activities of insulin, C-peptide, albumin, albumin/globulin ratio and restored all marker enzymes to near control levels. Accordingly, *Hibiscus rosa-sinensis* extract has an antihyperglycaemic effect and alleviated liver and renal damage associated with streptozotocin-induced diabetes mellitus in rats[96].

The hypoglycemic activity of the ethanol extract of *Hibiscus rosa-sinensis* was studied in rats. After a single dose of the extract, a slight but insignificant hypoglycemic effect was observed at 30 and 90 min, at 120 min it was mild but significant. After repeated administration of the extract (once a day for seven consecutive days) a statistically significant ($P<0.001$) reduction in blood glucose levels was observed at 30, 90 and 120 min

after glucose loading. The average hypoglycemic activity, after repeated administration of 250 mg/kg leaf extract was 81%, under similar conditions, the average activity of tolbutamide was 96%. At 250 mg/kg, the efficacy of the extract was found to be 84% of tolbutamide (100 mg/kg). Repeated treatment of animals either with tolbutamide a sulphonylurea or *Hibiscus rosa-sinensis* caused a 2-3-fold improvement in glucose tolerance as compared to those receiving only once[97].

The antidiabetic effect of *Hibiscus rosa-sinensis* flower powder was studied in type II diabetic patients. 2g flower powder of *Hibiscus rosa-sinensis*, daily for 60 day significantly decrease level, mean fasting blood glucose, post prandial blood glucose level, mean glycosylated Hb level, mean total cholesterol, triglyceride level, total LDL and total VLDL cholesterol level[53].

Because fraction-3 (F3) and fraction-5 (F5) were more effective fractions among 5 fractions obtained from the ethanolic extract of *Hibiscus rosa-sinensis* leaves, they were used to study their anti-diabetic properties in non obese diabetic mice. Serum glucose, glycosylated hemoglobin, triglyceride, cholesterol, blood urea, insulin, LDL, VLDL, and HDL were estimated. Both fractions F3 and F5 (100 and 200 mg/kg bw) demonstrated insulinotropic nature and protective effect in non obese diabetic mice[98].

The hypolipidimic activity of flowers extract of *Hibiscus rosa-sinensis* was studied in alloxan induced diabetic rats. Oral administration of flowers extract in doses 50,100 and 200 mg/kg po, showed significant improvement in dyslipidemia caused by diabetes mellitus as evidenced by reduced level of total cholesterol, triglycerides, VLDL, LDL and elevated in HDL levels significantly[99].

The effect of ethanolic extract of *Hibiscus rosa-sinensis* (EHBS) leaves on alloxan-induced diabetes with dyslipidemia was studied in rats. Treatment of alloxan-induced diabetic rats with 2.0 mg/kg bw of EHBS for 1 week significantly reduced glucose level, TC, TG and LDL-C, and increased HDL-C and weight of kidney, pancreas and liver compared with diabetic rats. A similar results were obtained when the treatment of alloxan-induced diabetic rats continued for 4 weeks. EHBS leaves extracts, in comparison with metformin, possessed profound hypoglycemic and hypolipidemic activities[100].

The antidiabetic, hypolipidimic, antioxidant and histopathological effects of *Hibiscus rosa-sinensis* were investigated in alloxan induced diabetes in rats. HEFHR (hydroalcoholic extract of flower of *Hibiscus rosa-sinensis*, 50-200 mg/kg bw) possessed significant and sustained antidiabetic activity, comparable with the hypoglycemic effect of glibenclamide and sulphonylurea. Flower extract of HRS was more efficacious in lipid lowering effect and in antioxidative activity than glibenclamide. After 28 day treatment with flower extract, size of islets was significantly increased and necrosis and atrophy of islets were significantly improved; also increase in number and diameter of cell islets compared to the diabetic group[101].

Blood glucose and total lipid levels were determined in streptozotocin induced diabetic rats after oral administration of an ethanol flower extract of *Hibiscus rosa-sinensis*. Ethanol flower extract possessed hypoglycemic effect after 7 and 21 days of oral administration of the extract. Maximal diminution in blood glucose (41-46%) was noticed after 21 days. The extract lowered the total cholesterol and serum triglycerides by 22 and 30%, respectively. HDL-cholesterol was much higher increased (12%) by the extract compared to glibenclamide (1%). The hypoglycemic activity of this extract was comparable to that of glibenclamide but was not mediated through insulin release[102].

The hypolipidemic activity of *Hibiscus rosa-sinensis* root extract was studied in triton and cholesterol-rich high fat diet (HFD) induced models of hyperlipidemia in rats. Root extract (500 mg/kg bw/ day orally), possessed lipid-lowering effect , as assessed by reversal of plasma levels of total cholesterol (TC), phospholipids (PL) and triglycerides (TG) and reactivation of post-heparin lipolytic activity (PHLA) of plasma in triton model. The root extract (500 mg/kg bw/ day orally) for 30 days also lowered the lipid levels in plasma and liver homogenate and reactivation of plasma PHLA and hepatic total lipoprotein lipase activity in cholesterol-rich high fat diet model[103].

Cytotoxic effect:

Hibiscus rosa-sinensis extract possessed a protective effect against the tumour promotion stage of cancer development. The ameliorative potential of *Hibiscus rosa-sinensis* extract was investigated in hyperproliferation and oxidative damage caused by benzoyl peroxide and ultraviolet radiations in mouse skin. Pretreatment with *Hibiscus rosa-sinensis* extract (3.5 mg and 7 mg/ kg bw) partly restored the levels of cellular protective enzymes ($P<0.05$). Besides, malondialdehyde formation and hydrogen peroxide content ($P<0.05$) were statistically significantly reduced at both doses. The ornithine decarboxylase activity and thymidine incorporation in DNA were also reduced, dose dependently ($P<0.05$) by the plant extract[104].

The role of gentisic acid in the chemopreventive activity of *Hibiscus rosa-sinensis* extract was studied in 7,12-dimethyl benz(a)anthracene (DMBA)/croton oil-mediated carcinogenesis in mouse skin via 12-O-tetradecanoyl phorbol-13-acetate (TPA)-induced tumour promotion response and oxidative stress. Application of *Hibiscus rosa-sinensis* extract 30 minutes prior to the application of croton oil twice weekly for 20 weeks caused significant reduction in the number of tumours per mouse and the percentage of tumour-bearing mice.

The latency period for the appearance of the first tumour was delayed on *Hibiscus rosa-sinensis* pretreatment. Pretreatment of *Hibiscus rosa-sinensis* extract (3.5 mg and 7 mg/kg bw) and gentisic acid (2.0 microg and 4.0 microg/0.2 ml acetone per animal) restored the levels of GSH, and its metabolizing and antioxidant enzymes ($P<0.05$). There was also a statistically significant reduction in MDA formation and H_2O_2 content ($P<0.05$) at both doses. The authors postulated that gentisic acid has a role in the modulatory activity of *Hibiscus rosa-sinensis* extract[105].

The *in vitro* cytotoxic activity of the crude petroleum ether, ethyl acetate and methanol extracts of the leaf and stem of *Hibiscus rosa-sinensis* (20 - 100 µg/ml) was evaluated against leukaemic cancer cell line (K-562). The methanol leaf extracts showed higher activity (IC_{50} value: 30.9 ± 1.1 µg/ml) against K-562 cells than petroleum ether and ethyl acetate extracts which exhibited IC_{50} of 87.6 ± 0.91 and 57.6 ± 0.61 µg/ml ($P<0.05$), respectively. Meanwhile, stem methanol extracts showed IC_{50} of 79.80 µg/ml against K-562. The methanol extracts produced cell death on K-562 cells by apoptosis[106].

The cytotoxic activity of aqueous and chloroform extracts of flowers of *Hibuscus rosa-sinensis* was investigated against MCF-7 cell lines using MTT assay. Extracts possessed marked % inhibition of cell viability against MCF-7 cell lines in dose dependent manner. The mean IC_{50} values of chloroform extract was 46.1±2.816% and 61.88 ±0.662%, and aqueous extract 42.91 ±0.104% and 56.29 ±0.083% at concentration of 100 and 200 µg/ml respectively[107].

The aqueous extracts of *Hibiscus rosa-sinesis* flowers inhibited melanoma cell growth in a dose dependent manner at concentrations that did not affect the growth of nontransformed cells. In addition, these extracts contained low molecular weight growth inhibitory compounds below 3 kD in size[108].

Antimicrobial effect:

The antibacterial activity of *Hibiscus rosa-sinensis* flower extract was studied against human pathogens. The results showed that the cold extract possessed a maximum zone of inhibition against *Bacillus subtillis* and *Escherichia coli* (17.00 ± 2.91 and 14.50 ± 1.71) mm respectively, followed by hot extraction against, *E. coli* and *Salmonella* sp. (11.66 ± 3.14 and 10.60 ± 3.09) mm respectively. Methanol extract showed a highest zone of inhibition against *B. subtillis* and *E. coli* (18.86 ± 0.18 and 18.00 ± 1.63) mm respectively, while ethanol extract showed utmost zone of inhibition against *Salmonella* sp. at (20.40 ± 1.54) mm. The crude protein from flower showed a maximum inhibitory zone against *Salmonella* sp. and *E. coli* (16.55 ± 1.16 and14.30 ± 2.86) mm respectively[109].

The methanol, chloroform, n-hexane and aqueous extracts of *Hibiscus rosa-sinensis* (25, 50 and 100 mg/ml) showed antibacterial activity against *Staphylococcus epidermidis* (11-23mm), *Bacillus subtilis* (13-26mm) and *Escherichia coli* (12-24mm). The extracts also possessed antifungal activity against *C albicans* (12-20 mm), *A flavus* (10-17mm) and *C glabreta* (0-19mm). It appeared that the methanolic extract was the most potent antibacterial and antifungal extract, its diameters of inhibition for the concentration of 100, 50 and 25 mg/ml were 20-26mm against *Bacillus subtilis*, 17-24mm against *Escherichia coli*, 19-23mm against *Staphylococcus epidermidis*, 15-19mm against *C glabreta*, 14-17 mm against *A flavus* and 15-20 mm against *C* albicans[110].

The crude petroleum ether extract, ethyl acetate extract and methanol extract from the leaves, stems and flowers of the plant were tested at concentrations ranging from 4 mg/disc to 0.017 mg/disc against methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumonia.* The petroleum ether extract from the leaves, stems and flowers and methanol extract from the leaves showed inhibition zones with diameters > 12 mm against MRSA. The petroleum ether extract from flowers at concentrations of 4 mg/disc and 2 mg/disc displayed the strongest inhibition zones of 18.6 ± 2.85 mm and 18.5 ± 0.29 mm, respectively against MRSA compared with vancomycin 30 µg/ml (18.0 ± 0.10 mm)[111].

The antimicrobial activity of 70% methanolic extract of *Hibiscus rosa-sinensis* petals was studied against *Staphylococcus aureus, Escherichia coli, Bacillus subtilis, Pseudomonas aeruginosa* and *Proteus vulgaris*. *Hibiscus rosa-sinensis* showed antimicrobial activity against *E. coli* and *P. vulgaris* with a zone of inhibition of 17.06 and 18.96mm respectively at the concentration of 20µl/ml[112].

Hibiscus rosa-sinensis leaves and flowers 95% ethyl alcohol extracts (20 µl extract/disc) possessed anti-*Shigella dysenteriae* effect (diameter of zone of inhibition of 11 and 12 mm respectively)[113].

The antibacterial activity of the extracts of *Hibiscus rosa-sinensis* leaves and flowers was studied against some clinical bacterial isolates. The extracts of *Hibiscus rosa-sinensis* flowers showed stronger antibacterial activity than that of leaves. The maximum zone of inhibition (29 mm) was observed against *S. aureus*, followed by *P. vulgaris* (25 mm), *P. aeruginosa* (24 mm) and *Citrobacter sp*. (24mm) and the lowest against *S. typhimurium* (13 mm) at the highest amount of flower extracts (100 mg/well). All the test bacteria

responded to the extracts in a dose-dependent manner. However, *K. pneumoniae* was found to be resistant to the flower extracts at the applied doses (50 and 100 mg/well) [114].

Antibacterial activity of crude extract of *Hibiscus rosa-sinensis* was evaluated against *Staphlococus* sp. *Bacillus* sp. and *Escherichia coli*, using agar disc diffusion method. The growth inhibitory diameters against *Staphlococus* sp. *Bacillus* sp. and *Escherichia coli* were in the range of 12.75 ± 1.17 to 16.75 ± 2.10 mm[73].

The antibacterial activity of *aqueous Hibiscus rosa-sinensis* flower extract was studied against *Escherichia coli* and *Bacillus subtillis*. The result showed that aqueous extract exerted high zone of inhibition against *Bacillus subtillis* 15.00 ± 2.81mm and *Escherichia coli* 12.50 ± 1.81mm. However, hexane extract showed the highest zone of inhibition against *B. subtillis* 19.86 ± 0.15mm and *E. coli* 18.00 ± 1.53 mm[115].

The antibacterial activity of the methanolic and ethanolic extract of *Hibiscus rosa-sinensis* petals was evaluated against dental pathogen, *Streptococcus mutans* in different concentration. The high concentration (300 µl methanol extract) of *Hibiscus rosa-sinensis* showed strong activity (27.33±1.632) against this pathogen[116].

The antimicrobial activity of *Hibiscus rosa-sinensis* extracts was examined against Gram positive and Gram-negative bacteria and fungal strains by measuring zone of inhibition. The leaf extract showed high activity against *Staphylococcus aureus* at very low concentration (2.5µg/ml) compared to *E.coli*, *Bacillus subtilis.* Leaf extract also showed high activity against *Candida parapsilosis* at a very low concentration (2.5µg/ml) compared to *Aspergillus niger.* The *Hibiscus rosa-sinensis* root extract showed high activity against all theted tes bacteria at very low concentration (2.5µg/ml). Root extract showed high activity against *Candida parapsilosis* and *Aspergillus niger* at a very low concentration (2.5µg/ml) compared to *Trichophyton rubrum.* The flowers extract showed activity against *E.coli* and *Staphylococcus aureus* (12 mm) at low concentration (2.5µg/ml). Flower extract also showed high activity against *Candida parapsilosis* and *Aspergillus niger* at a low concentration (2.5µg/ml)[57].

The antibacterial activities of crude petroleum ether extract, ethyl acetate extract and methanol extract of *Hibiscus rosa-sinensis* were studied (4 mg/disc to 0.017 mg/disc) against methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus aureus, Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumonia*. The petroleum ether extract from flowers at concentrations of 4 mg/disc and 2 mg/disc displayed the strongest antibacterial activity. The petroleum ether extract from the leaves, stems and flowers and methanol extract from the leaves showed inhibition zones with diameters > 12 mm against MRSA[111].

The methanolic leaf and flower extracts (31.25 to 500 mg/disc) were tested for antibacterial activity against *E.coli* and *S. aureus.* Both extracts showed increasing antibacterial property with increase in the extract concentration. The maximum zone of inhibition observed for both methanolic leaf and flower extracts of *H. rosa sinesis* at concentration of 500 mg against *E. coli* (23±1.01 and 13.75±0.99 mm), respectively. However, *against S.aureus,* methanolic leaf and flower extracts of *H. rosa sinesis* at concentration of 500 mg showed maximum zone of inhibition (19.33±0.29 and 9.75±0.76 mm)[60].

The antibacterial properties of *Hibiscus rosa-sinensis* flower extract was investigated against four Gram-positive (*Bacillus cereus, Bacillus subtilis, Staphylococcus aureus* and *Listeria monocytogenes*) and four Gram-negative bacteria (*Escherichia coli, Salmonella typhimurium Salmonella enteritidis* and *Klebsiella pneumoniae*). Aqueous extract of hibiscus inhibited the growth of *Salmonella typhimurium* (diameter of zone of growth inhibition: 11.5 and 9.0 mm at concentration of 100 and 50 mg/ml respectively), while ethanolic extracts inhibited the growth of *Staphylococcus aureus* (diameter of zone of growth inhibition: 14.0 12.0 mm at concentration of 100 and 50 mg/ml respectively)[117].

Antiparasitic effect:

The *in vitro* and *in vivo* anticestodal effects of methanol extract of *Hibiscus rosa-sinensis* leaf was investigated against *Hymenolepis diminuta*. *H. diminuta* worms were exposed to 10, 20 and 40 mg/ml concentrations of methanol leaf extract and the effects were judged on the basis of physical motility/mortality of worms. In *in vivo* study, *H. diminuta* infected rats were treated individually with 200, 400 and 800 mg/kg doses of leaf extract for 5 days. The effects were judged on the basis of reduction in eggs per gram (EPG) of faeces and worm counts. In *in vitro* test, the treatment with 40 mg/ml concentration of extract revealed prominent anticestodal effect and caused paralysis of worms in 3.00 ± 0.53 h and mortality in 4.08 ± 0.21 h. However, *in vivo* study revealed that 800 mg/kg dose of extract possessed the highest anticestodal effect and caused 66.55 % reduction in EPG count and 75.00 % reduction in worm count in the treated animals[118].

Dermatological effects:

The wound-healing activity of the ethanolic extract of the flowers of *Hibiscus rosa-sinensis* (5 and 10% w/w) was studied in rats using three different models (excision, incision and dead space wound). The extract increased cellular proliferation and collagen synthesis at the wound site, as evidenced by increase in DNA, total protein and total collagen content of granulation tissues. The extract-treated wounds were found to

heal much faster as indicated by improved rates of epithelialization and wound contraction. The extract of *Hibiscus rosa-sinensis* significantly (P<0.001) increased the wound-breaking strength in the incision wound model compared to controls. The extract-treated wounds were found to epithelialize faster, and the rate of wound contraction was significantly (P<0.001) increased as compared to control wounds. Wet and dry granulation tissue weights in a dead space wound model increased significantly (P<0.001)[119].

The efficacy and possible mechanism of the n-butyl alcohol extract of *Hibiscus rosa-sinensis* red flowers (NHRS) was investigated in wound healing using an excisional wound healing model in rats, different concentrations of NHRS, or recombinant bovine basic fibroblast growth factor (rbFGF), were applied twice daily for 9 days. Histopathology was assessed on day 9 using hematoxylin and eosin, Masson's trichrome staining, and immunohistochemistry for vascular endothelial growth factor (VEGF), transforming growth factor-β1 (TGF-β1) and CD68. Immunomodulation by NHRS was evaluated by a carbon clearance test in mice. NHRS accelerates wound repair via enhancing the macrophages activity, accelerating angiogenesis and collagen fiber deposition response mediated by VEGF and TGF-β1[120].

Healing enhancing effect of *Hibiscus rosa-sinensis* was assessed by the rate of wound contraction, period of epithelialization, tensile strength (skin breaking strength), granulation tissue weight, and hydroxyproline content. Animals treated with the extract exhibited an 86% reduction in the wound area compared with controls (75% reduction). The extract-treated animals were found to epithelize their wounds significantly faster than controls (P<0.002) and have shown significantly higher skin-breaking strength than controls (P<0.002). The dry and wet weight of granulation tissue and hydroxyproline content were also increased significantly when compared with controls[121].

The effect of *Hibiscus rosa-sinensis* (HRSF), *Calotropis gigantea* (CGF) and Polyherbal formulation. (HCF) (a combination of both plants extract, petroleum ether leaf extracts were incorporated into hair cream base prepared by fusion method) was investigated in stimulating hair growth in stress induced alopecia animal model in comparison with minoxidil. On comparison HRSF, CGF, HCF and minoxidil, it has been observed that HRSF as well as HCF herbal formulation application showed better growth that the patch with minoxidil. The hair growth studies revealed that HRSF possessed excellent hair growth promoting activity by an enlargement of follicular size and a prolongation of the anagen phase. The hair growth activity was also observed in CGF but less in comparison to HRSF, while the hair growth activity in animals treated by a combination of both extracts was found to be significantly increased when all the groups were compared statistically[122].

The petroleum ether extract of leaves and flowers of *Hibiscus rosa-sinensis* was evaluated for its effect on hair growth by *in vivo* and *in vitro* methods. *In vivo*, 1% extract of leaves and flowers in liquid paraffin was applied topically over the shaved skin of rats and assessed for 30 days. The length of hair and the different cyclic phases of hair follicles, like anagen and telogen phases, were determined at different time periods. *In vitro*, the hair follicles from rat neonates were isolated and cultured in DMEM supplemented with 0.01 mg/ml petroleum ether extract of leaves and flowers. The results revealed that the leaf extract exhibited more potency on hair growth when compared to flower extract[123].

The effect of ethanolic extract of *Hibiscus rosa-sinensis* leaves was studied on androgenic alopecia. The animals treated with testosterone and vehicle become alopecic from the second week of treatment, while animals treated with finasteride and ethanolic extract of *Hibiscus rosa-sinensis* did not become alopecic, the follicular morphology gave further evidence to hair growth stimulatory effects[124].

The ethanolic extract of *Hibiscus rosa-sinensis* flower was evaluated as hair growth promote in female rats. Skin was denuded with hair removing cream, electronic shavers and hair clippers for ensuring complete removal of hair. Then 2% solutions of *Hibiscus rosa-sinensis* flowers were applied on shaved denuded skin twice a day for thirty days. During this period they were observed visually for pattern of hair growth studies and after treatment period their skin biopiosis were taken for determination of follicular density and cyclic phases of hair growth. On the basis of visual observation of animals and histopathology, ethanolic extract of *Hibiscus rosa-sinensis* flowers showed shorter hair and take more time for growth and favours telogenic stage of hair follicles as compared to control thus it showed hair growth retarding activity inspite of hair growth promoting one[55].

Antioxidant effect:

Antioxidant potential of different solvent extracts of *Hibiscus rosa-sinensis* was evaluated by estimation of total flavonoids contents, total phenolic contents, DPPH free radical scavenging activity and percentage inhibition of linoleic acid oxidation capacity. Methanol and ethanol extract of *Hibiscus rosa-sinensis* showed total phenolics 61.45 ± 3.23 and 59.31 ± 4.31 mg/100g as gallic acid equivalent, total flavonoids 53.28 ± 1.93 and 32.25±1.21 mg/100g as catechine equivalent. DPPH free radical scavenging activity was 75.46±4.67 and 64.98 ± 2.11% and inhibition of linoleic acid oxidation potential 75.8 ±3.22 and 61.6 ± 2.01% respectively[73].

The antioxidant activity of *Hibiscus rosa-sinensis* flowers was evaluated *in vitro*. The flower extract exhibited antioxidant, hydrogen peroxide and superoxide radicals scavenging activities with IC_{50} values of 28.41±1.7, 36.69±2.3 and 32.32±2.5 µg/mL, respectively[66].

The crude water-ethanolic extract of *Hibiscus rosa-sinensis* leaves were investigated with various antioxidant systems. The results indicated that *Hibiscus rosa-sinensis* possessed abundant phenolic and flavonoids contents and exhibited excellent antioxidant activities comparing to synthetic antioxidants, butylated hydroxytoluene and butylated hydroxyanisole (BHT, BHA). The total phenolic and the total flavonoids contents of *Hibiscus rosa-sinensis* leaves extract reached 48.4 mg catechol equivalent and 24.26 mg quercetin equivalent /g dry weight, respectively[125].

The crude 90% methanolic extract of the leaves of *Hibiscus rosa-sinensis* possessed strong concentration dependent antioxidant activity. The methanolic extract of *Hibiscus rosa-sinensis* leaves also showed high ferric reducing antioxidant power[61].

Radical scavenging activity of the flower extracts of *Hibiscus rosa-sinensis* were determined based on the percent inhibition of DPPH and ferric reducing antioxidant power (FRAP) assays. The results showed that the flower extract contained high amount of antioxidant compounds and exhibited significant antioxidant activities, depended on extraction solvents. Aqueous extract of hibiscus had high tannin and anthocyanin contents, and showed high ferric reducing antioxidant power[117].

The anti-oxidant and antigenotoxic effects of ethanol extract of *Hibiscus rosa-sinensis* (HRS) flower was studied by evaluation of the potential of the extract to scavenging the free radicals and inhibiting lipid peroxidation *in vitro*. The ethanol extract showed a dose dependent increase in radical scavenging ability against various free radicals and also exhibited a significant inhibition of lipid peroxidation *in vitro* [126].

Hibiscus rosa-sinensis petals extracts were investigated for antioxidant using reducing power assay, metal chelating assay, antioxidant activity of hemoglobin induced linoleic acid and scavenging of hydrogen peroxide activity. The flavonoid rich fraction of petals of *Hibiscus rosa-sinensis* showed effective antioxidant activity in all assay techniques[112].

Antiinflammatory, antipyretic and analgesic effects:

The antiinflammatory activity of ethanolic extract of *Hibiscus rosa sinesis* (125, 250 and 500 mg/kg) was evaluated using carrageenin induce paw edema, cotton pellet induce granuloma and xylene induce mice ear edema. The analgesic activities were analyzed using formalin test and writhing test; the antipyretic effect was tested by pyrexia induced by brewer's yeast in rats. The ethanolic extract showed significant anti-inflammatory, analgesic and anti-pyretic effect[127].

The anti- inflammatory activities of ethanol extract of flower and leaf of *Hibiscus rosa-sinensis* var *alba* (white hibiscus) and *Hibiscus rosa-sinensis* L. (red hibiscus) was determined using carrageena model. Carrageenan was injected subplantarly 30 min before administration of each extracts (5, 50 and 100 mg/kg). Dosing of 50 and 100 mg/kg of flower and leaf estracts of *Hibiscus rosa-sinensis* caused significant inhibition ($P<0.05$) of edema. Flower and leaf of *Hibiscus rosa-sinensis* var *alba* extract significantly inhibited ($P<0.05$) edema in all range of testing dose. The white hibiscus revealed more potent anti-inflammatory effects. All extracts at various concentration caused significant reduction ($P<0.05$) in polymorphonuclear leukocytes infiltration with white hibiscus also more potent than red hibiscus. All extracts showed significant reduction ($P<0.05$) in the duration of licking response, white hibiscus was also more potent inhibitor[128].

The methanolic extract of *Hibiscus rosa- sinensis* leaves (250 and 500 mg/kg bw, orally) was studied for anti-nociceptive (acetic acid-induced writhing response and tail flick method) and anti-inflammatory (carrageenin and dextran induced rat paw edema) activities. The methanolic extract possessed significant anti-inflammatory activity and significant dose-dependent analgesic activity[129].

The antipyretic activity of the root extract of *Hibiscus rosa sinesis*, was evaluated in yeast induced pyrexia and the analgesic potentials was investigated in tail flicking method in rats at a dose of 250mg/kg bw. The aqueous root extract showed significant antipyretic and analgesic activities[130].

The anti-pyretic activity of *Hibiscus rosa-sinensis* aqueous extracts was evaluated in fever induced by yeast suspension (intraperitoneally 0.1 g/kg bw in mice). The animals with fever were administered orally with aqueous extracts of *Hibiscus rosa-sinensis* (500 mg/kg of bw). The result of the study showed that *Hibiscus rosa-sinensis* aqueous extracts significantly ($P<0.05$) effective in combating fever[131].

Immunomodulatory effect:

The immunomodulatory activities of hydro-alcoholic extracts of dried flowers of *Hibiscus rosa-sinensis* (75, 150 and 300 mg/kg, po) and dried leaves of *Euphorbia neriifolia* (100, 200 and 400 mg/kg, po) were studied using carbon clearance method, haemagglutination antibody titre method and footpad swelling method on Wistar albino rats. The results revealed that hydro-alcoholic extracts of dried flowers of *Hibiscus rosa-sinensis* possessed immunological effects, but the hydro-alcoholic extract of *Euphorbia neriifolia* exerted

more effect on immune components than hydroalcoholic extract of *Hibiscus rosa-sinensis* in dose dependent manner[54].

The aqueous extract of *Hibiscus rosa-sinensis* (AEHrs) (500 mg/kg bw) intraperitoneally injected to the house mouse (*Mus musculus*) male possessed immunological effects. After the 15 days treatment, the number of plaque forming cells increased by 0.6%, antibody titer increased 38.15% and significant increase of (52%) was observed in DTH response. At the same concentration of dose the level of serum IL-1alpha enhanced significantly (14.27%), whereas a considerable decrease (32.70%) in the concentration of IL-2 was observed among AEHrs treated mice in comparison to the control mice[132].

Central nervous effects:

The ethanolic extracts of flowers of *Hibiscus rosa sinesis* exhibited anticonvulsant activity. The bioassay guided fractionation indicated that the anticonvulsant activity attributed to the acetone soluble part of ethanolic extract of H. rosa sinesis flowers. The fraction protected animals from maximum electro shock, electrical kindling and pentylenetetrazole-induced convulsions in mice and inhibited convulsions induced by lithium-pilocarpine and electrical kindling. It antagonised the behavioral effects of D-amphetamine and potentiated the pentobarbitone-induced sleep. It raised brain contents of gamma-aminobutyric acid (GABA) and serotonin[133].

The antidepressant effect of crude ethanolic extract of floral part of *Hibiscus rosa-sinensis* (HRS) was studied at doses 100, 250 and 500mg/kg using three parameters [forced induced swimming test (FST), tail suspension test (TST) and open field test(OFT)]. Flouxetine (15mg/kg, bw) was used as standard. Significant dose dependent decline in immobility time was observed in all the three doses in FST and TST, while in OFT none of the doses of HRS showed significant effects. The results also revealed that all doses exhibited marked effect on MAO_A, while only 250mg/kg dose showed significant effect on MAO_B[134].

The antidepressant activity of methanol extract containing anthocyanins (MHR) (30 and 100 mg/kg) and anthocyanidins (AHR) (30 and 100 mg/ kg) of *Hibiscus rosa-sinensis* flowers were evaluated in mice using behavioral tests [tail suspension test (TST) and forced swim test (FST)]. The mechanism of action involved in antidepressant activity was investigated by observing the effect of extract after pre-treatment with low dose haloperidol, prazosin and para-chlorophenylalanine (p-CPA). The results revealed that extract caused significant decrease in immobility time in TST and FST, similar to that of imipramine (10 mg/kg, ip) which served as a positive control. The extract significantly attenuated the duration of immobility induced by haloperidol (50 μg/ kg, ip., a classical D2-like dopamine receptor antagonist), Prazosin (62.5 μg/kg, ip, an α1-adrenoceptor antagonist) and p-chlorophenylalanine (100 mg/kg, ip, × 3 days; an inhibitor of serotonin synthesis) in both TST and FST[135].

The ethyl acetate soluble fraction of the methanol extract of *Hibiscus rosa-sinensis* (EASF) attenuated amnesia induced by scopolamine and aging. The discrimination index (DI) was significantly decreased in the aged and scopolamine group in object recognition test (ORT). Pretreatment with EASF significantly increased the DI. In passive avoidance test (PAT), scopolamine-treated mice exhibited significantly shorter step-down latencies (SDL). EASF treatment showed a significant increase in SDL in young, aged as well as in scopolamine-treated animals. The biochemical analysis of brain revealed that scopolamine treatment increased lipid peroxidation and decreased levels of superoxide dismutase (SOD) and glutathione reductase (GSH). Administration of extract significantly reduced LPO and reversed the decrease in brain SOD and GSH levels. The administration of *Hibiscus rosa-sinensis* improved memory in amnesic mice and prevented the oxidative stress associated with scopolamine. This effect could be attributed to augmentation of cellular antioxidants[136].

An aqueous extract of *Hibiscus rosa-sinensis* showed 62.02%±0.03 inhibitory activity against AChE and 57.83%±0.05 inhibitory activity against BUChE enzymes. Accordingly, *Hibiscus rosa-sinensis* could be useful in improving memory and other cognitive function associated with the cholinergic system[137].

The effect of methanolic extract of *Hibiscus rosa-sinensis* (100-300 mg/kg) was studied on reserpine-induced orofacial dyskinesia and neurochemical alterations. Reserpine treated rats significantly developed vacuous chewing movements and tongue protrusions, coadministration of *Hibiscus rosa-sinensis* roots extract (100, 200 and 300 mg/kg, orally) attenuated the effects of reserpine. Biochemical analysis of brain revealed that the reserpine treatment significantly increased lipid peroxidation and decreased levels of superoxide dismutase (SOD), catalase (CAT) and glutathione reductase (GSH). Coadministration of extract significantly reduced the lipid peroxidation and reversed the decrease in brain SOD, CAT and GSH levels[138].

Cardiovascular effect:

The cardioprotective effects of dried pulverized flower of *Hibiscus rosa-sinensis* (150-200 g/kg, bw, orally) on isoproterenol induced myocardial injury was studied in rats. There was significant increase in the baseline contents of thiobarbituric acid reactive substances with both doses of *Hibiscus rosa-sinensis*. In the 250

mg/kg treated group, there was significant increase in superoxide dismutase, reduced glutathione, and catalase levels but not in the 125 and 500 mg/kg treated groups. Accordingly, *Hibiscus rosa-sinensis* (250 mg/kg) augmented endogenous antioxidant compounds of rat heart and also prevented the myocardium from isoproterenol induced myocardial injury[139].

The cardioprotective effects of *Hibiscus rosa-sinensis* (HRS) (applied at concentration of 90, 180, and 360 µg/ml for 15 minutes) were investigated in Langendorff- perfused rat hearts prior to 25-min global ischemia/120-min reperfusion (I/R). Only a moderate increase in LVDP (21% and 55%) and a tendency to increase CF was observed at HRS 180 and 360. HRS at 180 and 360 significantly improved postischemic recovery of LVDP, it dose-dependently reduced the numbers of ectopic beats and duration of ventricular tachycardia. HRS significantly reduced the infarct size at all concentrations in a dose-dependent manner[140].

The effect of the aqueous leaves extract (200 mg/kg) of *Hibiscus rosa-sinensis* was investigated on the renal function of hypertensive rats. Although *Hibiscus rosa-sinensis* leave extract reduced blood pressure, but it induced significant ($P<0.05$) increase in the Na^+ level of normotensive rats, thus it may interfere with the normal function of the kidney and hence increased salt retention[141].

Fibrinolytic effect:

The fibrinolytic effect of the aqueous extract of *Hibiscus rosa-sinensis* was studied and the fraction responsible for the fibrinolytc effect was investigated. The results showed that the extract of *Hibiscus rosa-sinensis* possesses greater fibrinolytic activity without haemolysis. The fraction 5 (among 11 fraction) of the extracts possessed the most significant fibrinolytic activity[142].

Anti-haemolytic effect:

The anti-haemolytic activity of *Hibiscus rosa-sinensis* flowers was investigated *in vitro*. The flower extract at various concentrations was incubated with erythrocytes and analysed for hydrogen peroxide induced haemolysis and lipid peroxidation as indices of erythrocyte damage. The extract significantly reduced hydrogen peroxide induced haemolysis and lipid peroxidation *in vitro*[66].

Urinary effect:

The aqueous extract of flowers of *Hibiscus rosa-sinensis* was evaluated for antilithatic potential *in vitro*. The presence of calcium oxalate crystals was evaluated immediately and after 24 hrs of stone induction. Crystal aggregation after 24 hrs was inhibited by *Hibiscus rosa-sinensis* extract. The extract interfered with early stages of stone formation and may represent an alternative form of treatment and or prevention for urolithiasis[143].

The effect of aqueous extract of *Hibiscus rosa-sinensis* on urinary volume and electrolyte extraction was studied in albino rats. Aqueous extract was administered in 100, 200, 400 and 600 mg/kg orally. Urine volume, total Na^+, K^+, Cl^- concentrations were estimated at 5^{th} and 24^{th} hr and compared with control group. Aqueous extract of *Hibiscus rosa-sinensis* increased the urine volume of the 5^{th} and 24^{th} hr samples. Na^+ and Cl^- excretion were also significantly increased in 200 and 400 mg/kg doses[144].

Protective effects:

Hibiscus rosa-sinensis petal partially purified anthocyanin extract possessed a hepato protective effects against carbon tetrachloride-induced lipoperoxidation[145-146].

The methanolic extract of *Hibiscus rosa-sinensis* flowers exhibited statistically significant ($P<0.005$) haemoprotective activity against phenylhydrazine induced haematotoxicity in Charles Foster rats[147].

The hepatoprotective potential of *Hibiscus rosa-sinensis* flower extracts (HRS) (acute: 80 160 and 240 mg / kg bw orally, once a day for 5 days, and chronic: the same doses for 30 days) was investigated in diet induced hypercholesterolaemic rat hepatocytes. The body weight was increased in cholesterol fed experimental animals which was reversed in HRS fed groups. There was a dose dependent increase in serum hepatic marker enzymes and total protein levels ($P>0.001$) in the cholesterol fed groups, which reversed with HRS flower extract fed acute ($P>0.005$) and chronic ($P>0.001$) groups. Increase in blood MDA level were seen in hypercholesterolaemic groups and significantly reduced ($P>0.05$) in HRS flower extract treated animals[148].

The protective effect of the alcoholic leaf extract of *Hibiscus rosa-sinensis* (AEH) (30 mg/kg bw for 15 days orally), was investigated against piroxicam-induced toxicity in mice. The results indicated that treatment with piroxicam alone (6.6 mg/kg bw for 15 days), resulted in a significant increase in the activities of aspartate transaminase, alanine transaminase, and alkaline phosphatase with profound hepatic lipid peroxidation as evidenced by a marked increment in the level of thoibarbituric acid reactive substances along with a distinct diminution in reduced glutathoine content and various antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase in the liver. AEH used in a combination with piroxicam treatment

retrieved or partially antagonized the effects induced by piroxicam toward the normal values. Histopathological observations also corroborated with the protective effects of AEH[149].

The neuroprotective potential of the methanol extract of *Hibiscus rosa-sinensis* (100, 200, 300 mg/kg/day for 6 days, po) was investigated in a bilateral common carotid artery (BCCA) occlusion model of global cerebral ischemic reperfusion. The bilateral common carotid artery occlusion resulted in increase in lipid peroxidation, and reduction in superoxide dismutase (SOD), catalase (CAT) and glutathione reductase (GSH) activity. The extract attenuated the ischemic reperfusion-induced increase in lipid peroxidation and fall in SOD, CAT, and GSH levels. The cerebral hypoperfusion caused a propensity towards anxiety and was accompanied by deficits of learning and memory. The extract ameliorated anxiety and improved learning and enhanced memory[150].

Effect in colitis:

The ameliorative effect of hydroalcoholic extract of leaves of *Hibiscus rosa-sinensis* (HRS) in acetic acid induced experimental colitis was investigated in male Wistar rats. Intrarectal instillation of acetic acid (2ml, 4%) enhanced ulcer area, ulcer index, spleen weight, colon weight to length ratio, colonic MPO, MDA, NO and TNF-α. It caused significant decrease in the level of SOD and GSH. Pretreatment with HRS for 7 days exhibited significant effect in lowering of oxidative stress, colonic NO, TNF-α and elevation of SOD and GSH at a dose of 100 and 200 mg/kg[151].

Antitussive effect:

The methanolic extract of *Hibiscus rosa-sinensis* was evaluated for antitussive activity in histamine chamber using citric acid (7.5%W/V) induced cough model. The methanolic extract of *Hibiscus rosa-sinensis* and codeine significantly decreased the number of coughing[152].

Toxicity and side effects:

The result of acute toxicity test revealed that maximum toxic dose was above 5 g/kg in mice, which indicated that the plant extract was relatively safe[127].

Administration of *Hibiscus rosa-sinensis* flower methanolic extract at doses of 100, 200, 400, and 800, mg/Kg in mice, did not produce any significant changes in behavior, skin effect, breathing, defecation, postural abnormalities, impairment in food intake and water consumption and yellowing or loss of hair[153].

Dosing of animals upto 500 mg/kg of all extracts caused no toxicity in rats. No significant changes ($P>0.05$) in liver enzyme levels and no histologically lesions in the organs[154].

The oral acute and subacute toxicity of methanol leaf extract of *Hibiscus rosa-sinensis* were investigated in mice. In the acute treatment, a single oral dose of 2000 mg/kg of extract gave to mice at 48 h intervals, did not reveal any signs of toxicity or mortality in any animal during the 14 days observation period. The LD_{50} of extract was estimated to be greater than 2000 mg/kg. In the sub-acute toxicity study, administration of 400 mg/kg and 800 mg/kg doses of extract to mice for two weeks did not reveal any marked adverse effects on hematological, biochemical parameters and histopathology of liver and kidney in the 400 mg/kg group. However, hepato-renal toxicity as evidenced by elevated levels of alanine aminotransferase, aspartate aminotransferase, total and indirect bilirubin, urea and creatinine was seen in the animals received 800 mg/kg dose of extract for 14 days. In addition, in the same group of animals, the histological assessments of liver and kidney also showed various adverse effects (dilated sinusoids, apoptotic nuclei and inflammatory infiltrate inside sinusoidal capillaries in the liver), and marked disorganization of tubules and glomeruli, and enlarged interstitial spaces in the kidney[51].

The genotoxic potential of the methanolic flower extract of *Hibiscus rosa-sinensis* was evaluated using micronucleus assay in Balb/c mice. *Hibiscus rosa-sinensis* showed no genotoxic activity in the micronucleus test. The frequency of micronuclei in groups of animals treated with *Hibiscus rosa-sinensis* showed no differences compared to the negative control (vehicle)[153].

The genotoxic effect of the ethanol extract was studied using a dose of 250mg/kg orally in mice (single dose and multiple doses repeated every 24 hr for 7 days). In additional, a group of mice (for subacute study), was administered after inducing genotoxicity with cyclophosphamide. The extract rendered significant ($P<0.001$) protection against cyclophosphamide induced genotoxicity in both micronucleus and comet assay indicating significant anti-genotoxic effects[126].

II. CONCLUSION:

The current review discussed the chemical constituents, pharmacological effects and therapeutic importance of *Hibiscus rosa-sinensis* as a promising medicinal plant with wide range of pharmacological activities which could be utilized in several medical applications because of its effectiveness and safety.

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