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MEDICINAL USES AND BIOLOGICAL ACTIVITIES OF *SOPHORA INTERRUPTA* BEDD-A REVIEW

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ABSTRACT

Sophora interrupta Bedd, was a common woody perennial herb native to India. Reports suggest that the plant possesses numerous health promoting benefits such as anticancer, antiinflammatory, antimicrobial and antioxidant activities. The plant exhibited several potential *in vitro* anticancer effects on MCF-7, PC-3, HeLa and HePG-2 cell lines. *In vivo* assay's suppressed in mouse models Dalton's lymphoma ascites, along with acute toxicity studies, central nervous system and hepatoprotective studies. The major phytoconstituents isolated from this plant are prenylated flavonoids, chalcones, biochanin-A and Kaempferol. This review aims to concern about taxonomy, cultivation, biological activities of the isolated compounds and to evaluate the current status of *S. interrupta* to give a comprehensive view of its future development and further improvement of its suitability in curing a wide range of ailments.

Keywords: *Sophora interrupta*, fabaceae, cancer, free radicals, cell lines.

INTRODUCTION

Approximately, more than 3000 plant species are officially documented for its medicinal potential in India[1]. Our traditional systems (3700 B.C) of medicines, viz., Ayurveda, Yunani, Siddha and Homeopathy etc. use herbs for treatment of wide range of ailments. It was estimated that 40% of the world populations depending directly on plant based medicine for their health care[2]. According to the WHO more than one million people rely on herbal medicines to some extent and also listed 21,000 plants for medicinal uses around the world [3]. India has a rich medicinal plant flora of around 150 species and were commercially used for extracting medicines or drug formulation [4]. *Sophora interrupta* belongs to Fabaceae family was a very important shrub in the Ayurveda and was highly studied by researchers in India.

Taxonomy: The taxonomic status of *S. interrupta* was well documented in table 1, Vernacular names: Adivibilla (Telugu), Pili Girgoli (Hawaiian). Synonyms: Edwardsia maderaspatana Wight.

Origin and geographical source: *Sophora* genus consists of approximately 36 species, distributed throughout the globe (*referring to table 2 with S.No*) which is clearly represented in the pictographic map (Figure 1). Tirumala hills are part of *Seshachalam hills* comprising of seven hills covered with dense forests situated very close to each other with plenty of Ayurvedic resources along with *S. interrupta*. The total area of Tirumala hills was about 4,755.99 sq. km. According to a study, it has been estimated that over 1,700 species belonging to 178 families of vascular plants exist in the region [http://www.thehindu.com/todays-paper/tp-in-school/rich-biodiversity-found-in-seshachalam-forests/article3989461.ece]. And this plant was endemically at higher altitudes such as at *Kumaradhara theertham*, *Sesha theertham*, *Kapila*

theertham and *Talakona* at sacred Tirumala hills [5, 6].

Morphological characteristics: *S. interrupta* grow to a height of two and half meters covered with golden yellow bell shaped flowers, comprising of auxiliaries and terminal racemes. Pods are four winged constricted between seeds. Seeds are 3-6, obovoid or globbose and strophiole. The roots are woody, tuberous, and perennial, about 4 to 8 cm in diameter, light brownish yellow in color with characteristic odor and highly bitter taste [7].

Propagation and planting: Species in this genus are spread throughout the tropical and temperate regions of the world. *S. interrupta* reported to flower at the time of the winter season [8]. Plantations which are planted apart from Tirumala are not propagating due to the absence of native soil and natural conditions i.e; endemic in nature (Unpublished observation).

Phytochemicals: Root and leaf extracts of this plant contains several phytochemicals such as, alkaloids, tannins, phenols, flavonoids, steroids, cardiac glycosides and saponins which were estimated using standard protocols. [7, 9].

PHARMACOLOGICAL ACTIVITIES

The generic name *Sophora* was derived from an Arabic word "*Sophera*" means a pea-flowered tree form. The leaf methanol extract of this plant suppressed Dalton's Ascitic Lymphoma in mouse models. Only few compounds from this plant were explored and if such medicinal plant correctly engaged in research will generate novel insights for treating various cancers. The current review aims to give the best of our knowledge on (i) the genetic diversity of the plant and Pharmacognostical studies. (ii) Biological role in disease targeting (iii) Isolated active components and its biological roles, which can show a bright research path for future generations.

***Sophora interrupta genetically diverse plant and Pharmacognostical studies*:** The plant *Sophora* genus was well explored all over the world almost 120 species. In which 57 species are still unexplored. *Sophora* species are well distributed from eastern part (Japan) to the western (Caribbean islands) part of the world. Most the species, *i.e.*; 36 from this genus are well explored with its geographical locations and its latitude and longitude of origins (table 2). Still, there is a need to explore and justify the putative compounds present in *Sophora interrupta* plant. Pharmacognostical studies explored the qualitative and quantitative microscopic evaluation of the root along with physicochemical parameters and fluorescence analysis of root powder which helps to establish diagnostic characters and quality parameters for the identification of the powdered form of root. TLC and HPTLC profile of Benzene extract was performed for flavonoids. Powder of root material showed the presence of xylem vessels with annular and scalariform thickenings, cork cells, starch grains and calcium oxalate crystals [7].

Biological role in disease targeting: *Sophora interrupta* was well reported to be in suppressing cancer cell growth in cell lines as well as in albino mouse models. All parts of the plant with different solvent extracts have been reported to have many biological activities which enables in potential applications such as in treating Cancer (*Dalton's lymphoma Ascites*) by leaf and whole plant methanol extract, cytotoxicity studies (*HeLa and HepG2*) cell lines by whole plant methanol extract, MCF-7 cancer cell lines, induction of apoptosis, and DNA fragmentation by leaf aqueous extract. Acute oral toxicity studies (*Albino mice*), ulcer (*Wistar rats*) by defatted methanol extract, central nervous system (CNS) on Swiss albino mice by the leaf methanol extract, the Anthelmintic activity of methanol leaf extracts on *Pheritima posthuma*. Hepatoprotective activity in Male Wistar rats by leaf methanol extract. However, reports on the biological activity on different diseases are clearly included below

Anticancer property: Dalton's lymphoma ascites (DLA) is a tumor which was developed in the thymus gland of a DBA/2 mouse at the National Cancer Institute, Bethesda, US in 1947. Later on, an ascites form was evolved by repeated intraperitoneal transplantation of tumor [10]. Dalton's lymphoma tumor cells were preserved in the ascites form by transplanting nearly 3×10^6 cells into the peritoneum of inbred Swiss albino mice. After 8-10 days a palpable tumor was observed and the tumor cells were taken out with the help of a syringe and a gauge needle. The *S. interrupta* leaf methanol extract was treated to DLA injected cancer model mice, at a drug of 100 mg/kg and 200 mg/kg body weight was orally administered (Figure 2) to the tumor bearing animals. Subsequently 15 days of treatment the extract diminished the body weight growth, reduction in packed cell volume, viable tumor cell count and the life span of mice was increased, serum enzyme, haematological parameters and lipid parameters were all at normal range values when compared to the cancer group mice, these findings suggested the leaf methanol extract at 200 mg/kg dose was protective against DLA [11]. However, one more research group also studied DLA, where the whole methanol

plant extract was examined haematological parameters in male Swiss albino mice in which 200 mg/kg and 400 mg/kg dose suggestively increased the Hgb content, RBC, platelets and decreased the WBC count to normal levels and also showed the percent increase of body weight [12]. All these results suggest this plant was highly anticancer in nature.

Anticancer activity in cell lines: Human cervical cancer (*HeLa*) is an immortal cell line taken first from Henrietta Lacks, a female patient died of cancer on Oct 4th, 1951and human hepatic carcinoma (*HePG2*) cell line which was a liver cell derived from 15-year-old Caucasian American male. The whole methanol extract of the plant was applied in two different cell lines (*HeLa & HePG2*) at different concentrations. Half minimal inhibition reported (IC_{50}) for *HeLa* 211.5 µg/mL and *HePG2* 158.2 µg/mL. This data suggests that this plant extract reduces the cervical and hepatic carcinoma cancers [13]. Michigan cancer foundation (MCF-7) breast cancer cell line was derived in 1970 from a 69-year-old Caucasian woman. MCF-7 cell lines taken from the patient Frances Mallon died in 1970 and it was unknown to the vast majority of cancer researchers. Her cells were the foundation of modern knowledge about breast cancer. Prostate cancer cells (PC-3) cell lines were established in 1979 from bone metastasis of grade IV of prostate cancer in a 62-year-old Caucasian male. Earlier we have reported that the root ethyl acetate extract of *S. interrupta* on both the cell lines shown significant DNA damage and was supported by the morphological changes such as membrane blebbing, cell detachment and rounded cell morphology when compared to the parental cells. In addition, we observed few green cells (live), over red cells (dead) based on the uptake of acridine orange and ethidium bromide dyes. DNA fragmentation assay was also reported in order to investigate the cell death mechanism in which the inter-nucleosomal breakdown of chromatin DNA, resulting in ladder-like agarose electrophoresis of degraded DNA. (Figure 3a & 3b) [14]. The apoptotic nucleus was found in a dose dependent manner, the shape of nucleolus completely vanished in at higher concentrations. Another research group reported on a leaf aqueous extract of *S. interrupta* against MCF-7 cancer cell lines to study antiproliferative and anticancer effects using MTT and LDH assays. Cells treated with *S. interrupta* extract, exhibited apoptotic morphological changes in dose dependent manner, such as cytoplasmic blebbing, enlarged, irregular-shaped, and vacuolated cytoplasm. These observations provide evidence that the compound present in the extract also trigger the apoptotic pathway. AO is a fluorescence dye that only stains live cells and EtBr is also a fluorescence dye stains orange dead cells, which interchelates with DNA. *In silico* analysis showed that Kaempferol-3-O-b-D-glucopyranoside, a Secondary metabolite of *S.interrupta* form 6 hydrogen bond interactions with Arg 202, Gln 207, Gly 227, Gly 229, Thr 231 and Ala 232 amino acids of human DEAD box RNA helicase (DDX3 protein). The nuclear condensation can be clearly seen from 100 µg/mL to 1000 µg/mL concentration. The treated cell nuclei appeared to be slightly smaller than normal nuclei, presuming these cells have tails nuclei with apoptotic bodies [9]. Ongoing research from our group reveals some important facts regarding the root extract of *S. interrupta*. From this 34 molecules from ethyl acetate extract were confirmed by GC-MS analysis. When all of them docked *in silico* against $VEGFR_1$ & R_2 proteins have shown good network of hydrogen bonding with Phe 1041, Asp 1040 for R_1 and Cys 919, Glu 917, Phe 1047, Lys 912 and Thr 916 for R_2 amino acids respectively. This extract when treated against blood vessels in the chick chorioallantoic membrane (CAM) has significantly reduced the intensity of forming blood vessels as a sign of antiangiogenic nature. The toxicity studies of this extract on brine shrimp's confirmed us that it was non-toxic and do not harm shrimps in any dosage forms.

Acute oral toxicity and ulcer studies: Acute oral toxicity was an adverse effect of a substance for single exposure or multiple. *S. interrupta* leaf defatted methanol extract was reported for acute oral toxicity in Swiss albino mice, the extract was not shown toxic reactions, behavior changes as well as mortality up to 2500 mg/kg and toxicity and mortality was gained at 5000 mg/kg and thus safe dose was considered to be 4000 mg/kg. Ulcer was a discontinuity in the membrane which hinders the normal function of the organ. Antiulcer studies were performed in Aspirin and ethanol induced male Wistar gastric ulcer rats using same extract, the extract showed significant reduction in Aspirin induced ulcer index (5.22+0.2) and ulcer formation (60.42%). Similarly ethanol induced gastric ulcer was reduced the ulcer index (5.2+0.1) and ulcer formation (60.42%) [5].

Sophora interrupta activity on CNS: CNS is a part of the nervous system consisting of the spinal cord and brain. *S. interrupta* leaf methanol extract was documented for Central Nervous System (CNS) activity. A daily dose of 200mg/kg of extracts was administered respectively to the swiss albino mice for 15 days, after which head dip test reported that

exploratory behavior shown to be reduced, traction tests and the rota rod test revealed the reduction in the motor co-ordination of the tested animals when compared with the control animals. The results revealed that the methanol leaves extract of *S. interrupta,* caused significant marked decline in exploratory behavioral pattern in head dip test at 58.88 % protection, and a reduction in muscle relaxant activity also observed by rota rod 55 % protection and traction tests 55.02 % protection [15].

Anthelmintic activity of methanol leaf extract: Helmintic parasites are cellular organisms, usually can be seen with naked eyes in their mature stage. They are worm-like organisms exists, and feed on living host's nutrient absorption, causing weakness and diseases. In order to address this issue a research team worked on leaf methanol extract against *Pheritima posthuma* (model for Anthelmintic studies). Results reported that within less time the worms went paralyzed, i.e; at concentration 30 mg/mL extract has taken less time to cause paralysis when compared with the standard [16].

Hepatoprotective activity: Chemicals that cause liver injury are called hepatotoxins. There are many chemicals and drugs which on over dosage lead to hepatotoxic. The hepatoprotective activity was well documented with the Leaf methanol extract against carbon tetrachloride induced hepatotoxic male Wistar rats [17]. The alterations in the serum markers such as alkaline phosphatase (ALP), aspartate transaminase (AST), alanine aminotransferase (ALT), and total bilirubin resembles hepatotoxic nature. Treatment with the methanol extract at a concentration of 400 mg/mL exhibited protection in altering the serum levels and also supported the work with Histopathological studies of liver sections. Hence *S. interrupta* proves one of the herbal metabolite for treating liver dysfunctions.

Isolated active components and its biological roles: A few of biologically active compounds, including phenols, flavonol's and flavones have been isolated from roots of the plant. These compounds have been reported to have different biological roles in disease conditions, thus enabling potential application in clinical research. A novel compound has been isolated from the roots, (Figure 4) such as O-prenylated flavonol i.e; *3′, 4′-dimethoxy-7-(γ, γ-dimethylallyloxy) flavonol*. *2′-hydroxy-3, 4-dimethoxychalcone* was a well-known natural phenol. *Biochanin A* was an isoflavone and well explored. *Kaempferol-3-O-β-D-glucopyranoside* was also a natural flavonol. These all compounds are structurally elucidated by ^{1}H and ^{13}C-NMR [18].

a) *3′, 4′-dimethoxy-7-(γ, γ-dimethylallyloxy) flavonol*, which was an O-prenylated flavonol its molecular mass 383.1451 and its molecular formula $C_{22}H_{22}O_6$. Although it was reported that it was extracted from *S. interrupta*, its biological activity was yet to be explored. Generally flavonol sub class of flavonoids possess phytoestrogenic or antioxidant properties [19]. For example a prenylated flavonoid was isolated from *S. flavescens* shown significant inhibition of acetyl cholinesterase activity [20].

b) *2′-hydroxy-3, 4-dimethoxychalcone* its molecular mass 284.306488 g/mol and molecular formula $C_{17}H_{16}O_4$. These chalcones are open chain flavonoids possess a wide range of pharmacological activity such as antibacterial, antitumor, anticancer, ant tubercular, anti-inflammatory, antioxidant, antimalarial, antileishmanial and also strong antioxidant activity [21]. Chalcones also possess cytotoxic activity on cancer cell lines [22].

c) *Biochanin A* was an O-methylated isoflavone. Its molecular mass 284.26 g/mol and its molecular formula $C_{16}H_{12}O_5$. *Biochanin-A* found in cloves, sprouts, peanuts, etc. It has putative benefits towards cancer prophylaxis [23].

d) *Kaempferol-3-O-β-D-glucopyranoside* was first isolated from *Phytolacca americana* plant source and later it was also isolated from *S. interrupta*. It was also known as Astragalin, with a molecular mass 448.37 g/mol and the molecular formula $C_{21}H_{20}O_{11}$. The biological activity reported to be a highly antiinflammatory effect and show good antioxidant activity with DPPH stable free radicals [24].

CONCLUSION

The current review reveals in a very interactive manner, showing geographical region, parts used, mechanism of action found to be having potent anticancer, antiproliferative, antioxidant, anthelmintic and CNS activities. This plant has been reported to contain phytoconstituents such as prenylated flavonoids, chalcones, biochanin-A and Kaempferol. The compounds which were isolated from this plant have pharmacological and toxicological investigations both *in vitro* and *in vivo.* And these can be lead molecules in human clinical trials. Thereby, the review can help researchers to know the work done so far on *S. interrupta*. It further helps in modern drug development and serves the purpose of Ayurvedic formulation development in treating diseases by proving clinical safety, reliability and efficacy.

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CONFLICT OF INTEREST
The authors have no conflicts of interest to declare.

Table 1: Taxonomic status of *Sophora interrupta*

Domain	**Eukaryota**
Kingdom	Plantae
Sub-kingdom	Viridaeplantae
Phylum	Tracheophyta
Class	Spermatopsida
Sub-class	Magnoliidae
Super Order	Rosanae
Order	Fabales
Family	Fabaceae
Subfamily	Faboideae
Tribe	Sophoreae
Genus	Sophora
Species	interrupta

Table 2: Different *Sophora* species with geographical locations in worldwide

S. No	**Sophora species**	**Geographical location**	**Latitude & Longitude**
1	*S. interrupta*	Tirumala hills	13.6 & 79.3
2	*S. microphylla*	a) Chatham Island, Chile b) Gough Island.	a) -50.4 & -72.7 b) -40.3 & -9.9
3	*S. alopecuroides*	Karachi	25.01 & 67.06
4	*S. viciifolia*	Yun-Nan; China	25.1 & 101.8
5	*S. tomentosa*	a) Tokyo; Japan. b) Texas; U.S.A	a) 35.6 & 139.7 b) 31.1 & -100.0
6	*S. tetraptera*	Landcare Research; New Zealand	-43.6 & 172.4
7	*S. subprostrata*	Shimizu-shi Shizuoka; Japan	35.08 & 138.5
8	*S. secundiflora*	a) Amistad Recreation Area near Del Rio, Texas. b) Peshawar; Pakistan.	a) 29.4 & -101.05 b) 33.9 & 71.5
9	*S. prostrata*	New Zealand	-43.3 & 172.4
10	*S. leachiana*	USA	-37.6 & -95.66
11	*S. koreensis*	Incheon, South Korea	37.4 & 126.6
12	*S. exigua*	Thailand	13.03 & 101.4
13	*S. fraseri*	Benth; Australia	-41.5 & 147.7
14	*S. stenophylla*	Hildale, Washington County, UT	37.01 & -112.9
15	*S. nuttalliana*	West of Cedar City, Iron County, UT	37.6 & -113.1
16	*S. mollis*	Peshawar; Pakistan	33.9 & 71.5

17	*S. macrocarpa*	La Dormida Paes, North of Santiago, Chile	-33.6 & -70.3
18	*S. japonica*	a) Nanjing, (People's Republic) China. b) University of California.	a) 32.0 & 118.7 b) 37.2 & -119.2
19	*S. flavescens*	a) Lanzhou, China b) Shanxi Province, China. c) Botanical Garden of Wonkwang University, Iksan, Korea. d) Seoul, Republic of Korea. e) Japan f) Transbaikalia and Primorsky regions and Agin Buryat Autonomous Okrug, Russia. g) Gansu Province, China. h) Taejon, Korea. i) Kangwon Province, Korea.	a) 36.0 & 103.7 b) 37.6 & 112.3 c) 35.9 & 126.9 d) 37.5 & 126.9 e) 37.4 & 136.4 f) 53.7 & 114.9 g) 37.6 & 100.5 h) 36.3 & 127.3 i) 37.8 & 128.2
20	*S. davidii*	Texas	31.1 & -100.07
21	*S. chrysophylla*	Pohakuloa; Hawaiian islands	23.5 & -166.7
22	*S. alopecuroides*	Xinjiang, China	41.7 & 84.9
23	*S. tonkinensis*	a) South China. b) Guangxi Province	a) 25.5 & 112.8 b) 23.6 & 108.2
24	*S. tetraptera*	Auckland, New Zealand	-36.8 & 174.8
25	*S. yunnanensis*	China	35.8 & 104.1
26	*S. velutina*	Zimbabwe National Herbarium	-19.01 & 29.15
27	*S. arizonica*	Mohave, Arizona, U.S.A.	35.6 & -113.6
28	*S. secundiflora*	Kingsville, Kleberg. Texas.	27.5 & -97.8
29	*S. gypsophila*	Edo. Chihuahua, Mexico	28.6 & -106.1
30	*S. exigua*	Northeastern Thailand	16.4 & 102.7
31	*S. toromiro*	Easter island	-27.1 & -109.3
32	*S. longicarinata*	New Zealand	-43.3 & 172.4
33	*S. fernandeziana*	Juan Fernandez islands	-33.6 & -78.8
34	*S. masafuerana*	Juan Fernandez islands	-33.6 & -78.8
35	*S. macnabiana*	Gough island	-40.3 & -9.9
36	*S. howinsula*	Lord howe island; Caribbean	-31.5 & 159.07

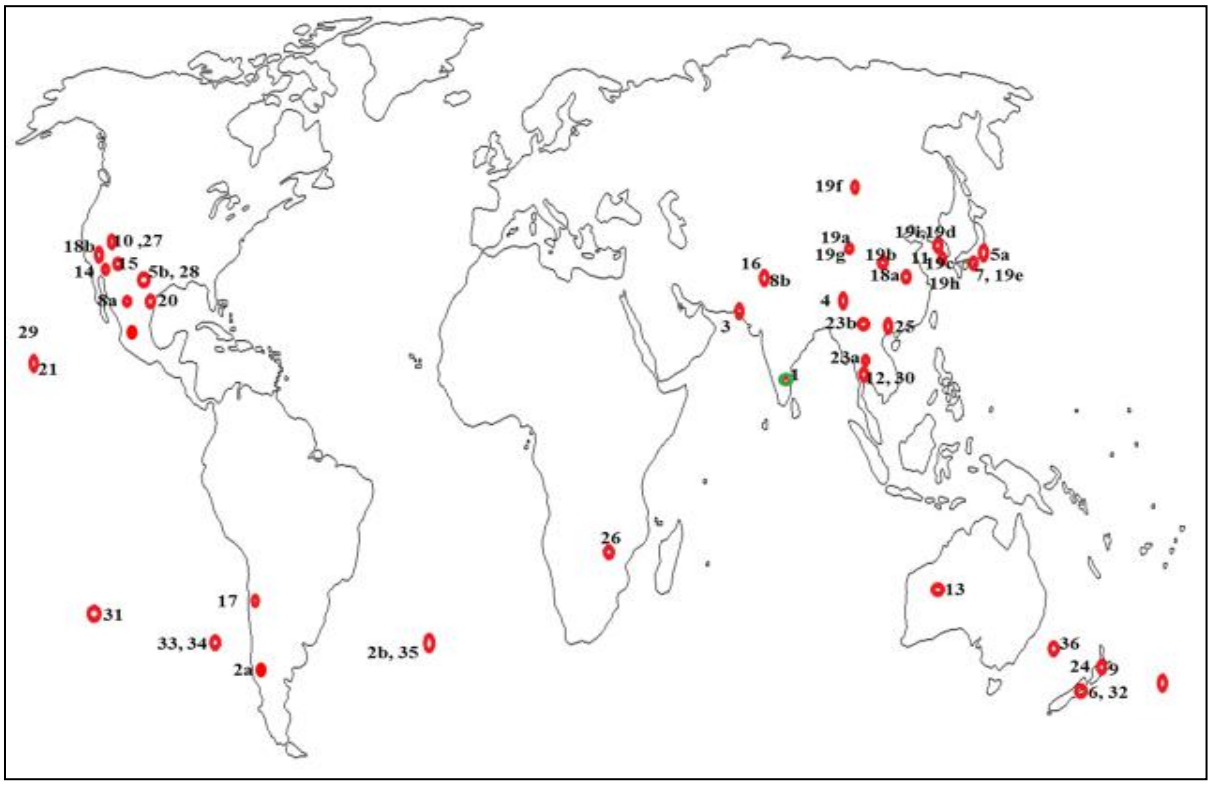

Figure 1: Pictographic representation of *Sophora* species in world map with serial numbers referring table 2

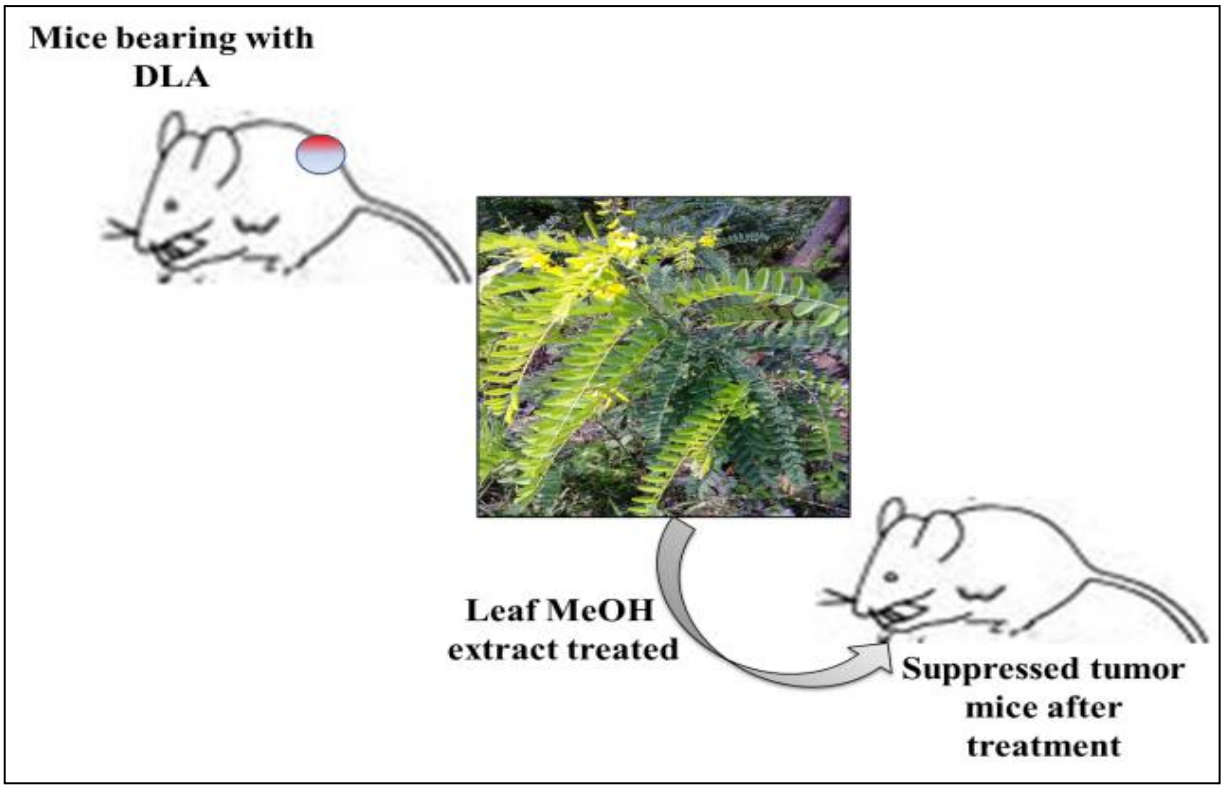

Figure 2: *Sophora interrupta* treating Dalton's Ascites Lymphoma (DLA)

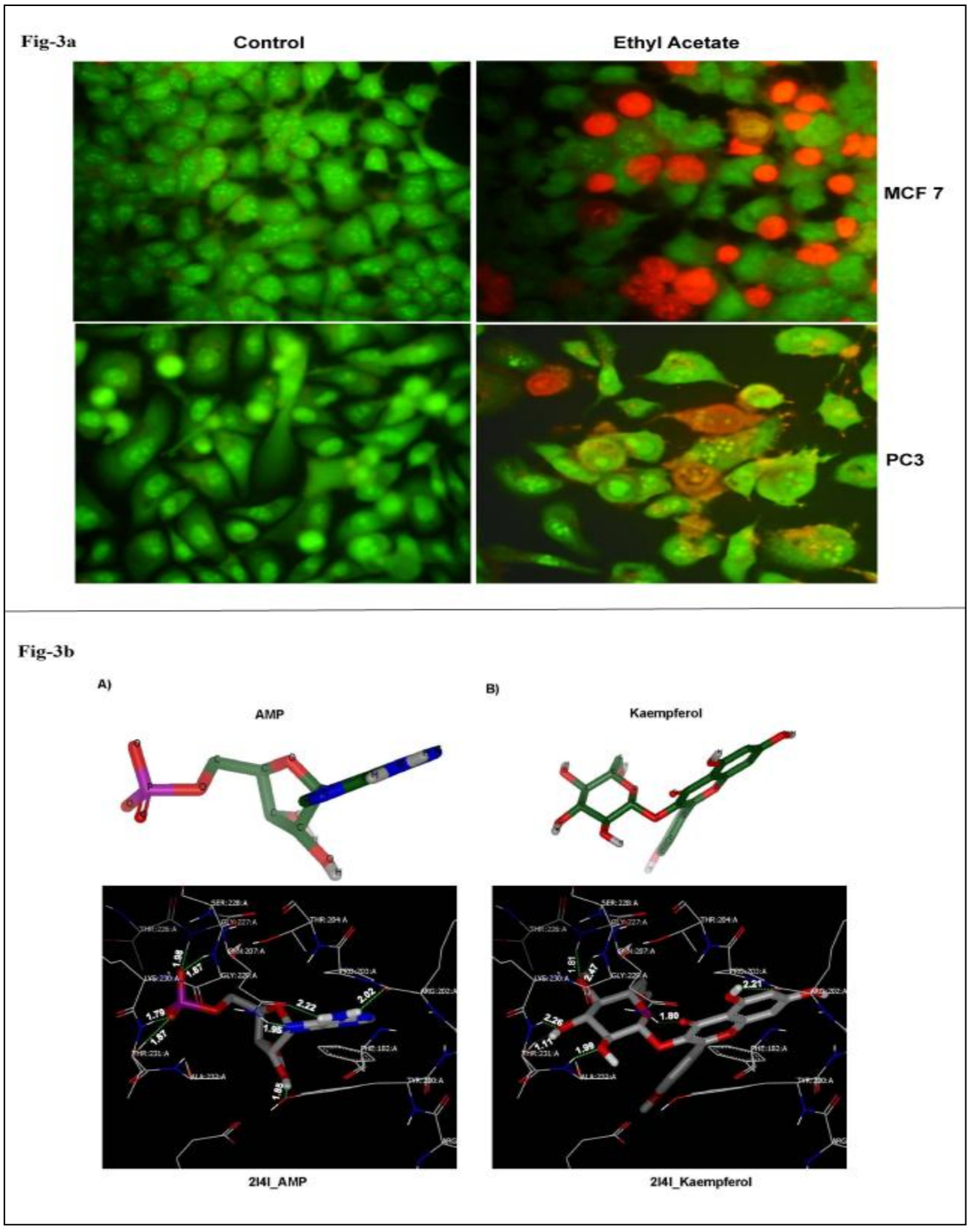

Figure 3: a) MCF-7 & PC-3 cells representing Apoptosis assay by Acridine orange/ Ethidium bromide. Early and late apoptosis depicted by orange and red colored cells. b) *Insilico* docking against DDX3 (PDB ID: 2I4I) with AMP; Kaempferol.

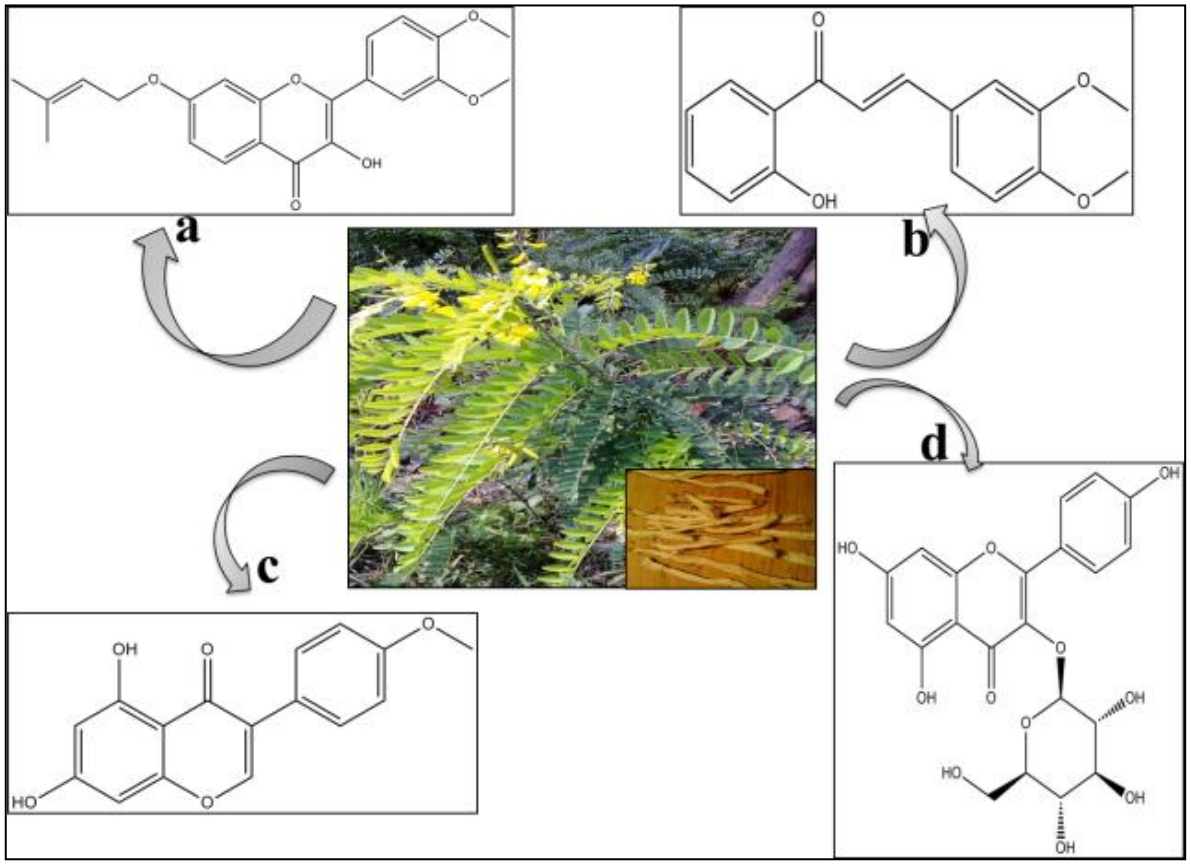

Figure 4. Compounds isolated from *S. interrupta* root are a) *3', 4'-dimethoxy-7-(γ, γ- dimethylallyloxy) flavonol* b) *2'-hydroxy-3, 4-dimethoxychalcone* c) *Biochanin A* d) *Kaempferol-3-O-β-D-glucopyranoside*

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