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A COMPREHENSIVE REVIEW ON SECONDARY METABOLITES OF *GLYCYRRHIZA GLABRA* AGAINST CANCER CELL LINES

HASE DP[1], DARANDALE S[2], BHAVSAR KS[3], PANDHARE GR[2], KADAM KR[2], UPHADE BK[2], MAHALE MV[1], MORE VS[1] AND MURADE V[2*]

1: Amrutvahini College of Pharmacy, Sangamner 422608, India

2: Padmashri Vikhe Patil Arts, Science and Commerce College, Pravaranagar, 413713, India

3: MGSM's Arts, Science and Commerce College, Chopda, Jalgaon, 425107, India

***Corresponding Author: Dr. Vaishali Murade: E Mail: vaishali.hase66@gmail.com**

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ABSTRACT

Cancer is nothing but the anonymous growth of tissues and improper vascular supply to the body. Plant based medicines are grabbing attraction as an efficient source of anticancer pharmacophores because of its easy availability, comparatively cheaper and least side effects. World Health Organization is nowadays encouraging the applications of ancient medicines having great efficiency and least toxicity. In present review attempted comprehensive study related to a plant having anticancer activities along with its chemical compositions such as flavonoids, saponins, curcuminoids, etc as well as its possible mechanism of action against carcinoma cell lines like, apoptosis via., intrinsic and extrinsic pathways, cell cycle disruption and the levels of various vital parameters-reactive oxygen species (ROS), vascular endothelial growth factor (VEGF) and cyclin dependent kinases (CDKs). The constituents from the different parts of *Glycyrrhiza glabra* are safe for its pharmaceutical implementation for the treatment of cancer and its variable mechanisms of action against different carcinoma cell lines are making it an efficient plant based pharmacological scaffold for the treatment of cancer.

Keywords: Carcinoma, apoptosis, *Glycyrrhiza glabra*, Reactive Oxygen Species, Vascular Endothelial Growth Factor

INTRODUCTION:

Cancer is one of the most lethal diseases in which uncontrolled growth of abnormal tissues in the body of an organism occurs. According to global cancer statistics 10 million deaths and more than 19 million new cases estimated in year 2020 **[1]**. There are several treatments available for cancer on the basis of its severity namely, radiation therapy, chemotherapy, hormonal therapy, stem cell transplant, immunotherapy etc. **[2]**. Amongst all these available treatments chemotherapy is the widely used but several side effects of this treatment like lack of selectivity, drug resistance, nausea, vomiting, anxiety, weight loss and lack of appetite are observed in various patients **[3]**. On the other hand, biologically active products isolated from the plants can be significantly used for the treatment of cancer because of their enhanced activity and decreased toxicity. Nowadays, plant-based treatments are widely used as efficient anticancer agents because of their applicability and pharmacological efficiency to a greater extent and also, they are extensively available in relatively cheaper price and have no major side-effects **[4]**. In present review attempted to recapitulate a medicinally important plant viz., *Glycyrrhiza glabra* Linn. its chemical composition, traditional uses and mechanism of action against cancer cells.

GLYCYRRHIZA GLABRA LINN.

One of the significant members of the Fabaceae family, *Glycyrrhiza glabra* Linn. commonly known as Mulaithi or Liquorice. It is a small perpetual herbaceous plant locally cultivated in several countries like India, Italy, Russia, Australia, America, China and Germany. It can be used as an efficient therapeutic agent and flavouring agent for masking the foul smell of other medications **[5]**. It has several pharmacological characteristics such as anti-allergic, anticancer, antidiabetic, anti-inflammatory, antiulcer, antipyretic, antioxidant and antiepileptic **[6-16]**. It makes utmost candidate for pharmacological research in near future. The phytochemical compositions, traditional uses and mechanisms of action as an anticancer agent of *Glycyrrhiza glabra* Linn. are summarized herein.

CHEMICAL COMPOSITION OF *GLYCYRRHIZA GLABRA LINN.*:

Flavonoids and isoflavonoids:

The *Glycyrrhiza glabra* L. generally consist of six major types of flavonoids namely, flavanones, chalcones, isoflavanes, isoflavenes, flavones and isoflavones **[17]**. Zhang and co-workers have successfully identified numerous flavonoids namely, liquiritin, liquiritigenin, rhamnolliuiritin,

liquiritinapioside, gralbranin, glabrol, licoflavanone, isoliquiritigenin, neoisoliquiritin, licuraside, licochalcone A/B, licoricidin, 7-methillicoricidin, hispaglabridin A/B, liocflavone A/B, liocflavanol, glyzaglabrin, licoisoflavanone, glabroisoflavanone, glabrone, licoricone, and gancaonin **[19]**. The analysis performed by Williamson effectively discovered the presence of various isoflavonoid derivatives like glabridin, galbrene, glabrone, shinpterocarpin, licoisoflavones A and B, formononetin, glyzarin and kumatakenin **[20]**. In past few years, several research related to the presence of isoflavonoids in *G. glabra* was performed and resulted presence of isoflavonoids such as 4'-O-methylglabridin and 3'-hydroxy-4'-O-methylglabridin and glabroisoflavanone A and B glabroiso-flavanone B are present in extracts of *G. glabra* **[21, 22]**.

Saponins:

Triterpenoid saponins; glycyrrhizin and glycyrrhizic acid are the prime components of *G. glabra* isolated from the roots. Amongst these, glycyrrhizic acid is responsible for the sweetness present in the roots of the plant **[23]**. The other triterpenes like liquiritic acid, glycyrretol, glabrolide, isoglaborlide, and liquoriceacid were identified by Isbrucker and Burdock **[24]**. The ethanolic extract of the plant showed the presence of ammonium glycyrrhizinate (3.4%) and calcium glycyrrhizinate (4%) **[25]**. In past few years, various saponins originated from Glycyrrhiza species such as licorice-saponin A3, 22β-actoxylglycyrrhizin, uralsaponin B, apioglycyrrhizin, araboglycyrrhizin, and licorice-saponin E2 were illustrated by Zhang and co-workers **[30]**.

Phenolic compounds:

The liquiritin, isoliquiritin, liquiritinapioside, flavonoids substituted with isoprenoid, chromenes, coumarins and dihydrostilbenes are the major phenolic components present in the Glycyrrhiza species **[27]**. A group of scientists studied the different Glycyrrhiza species for identification of its phenolic contents and revealed that flavonoids substituted with isoprenoid moiety namely, pyranoisoflavan and glabridin **[28]**. Ammar and co-workers analysed the highly polar extract of *G. glabra* and isolated several phenolic compounds like liquiriteginin, liquiritinapioside, neoliquiritinapioside, isoliquiritin, isoliquritinapioside, licuraside2-(5-*P*-coumaryl apiosyl), and isoliquiritin **[29]**.

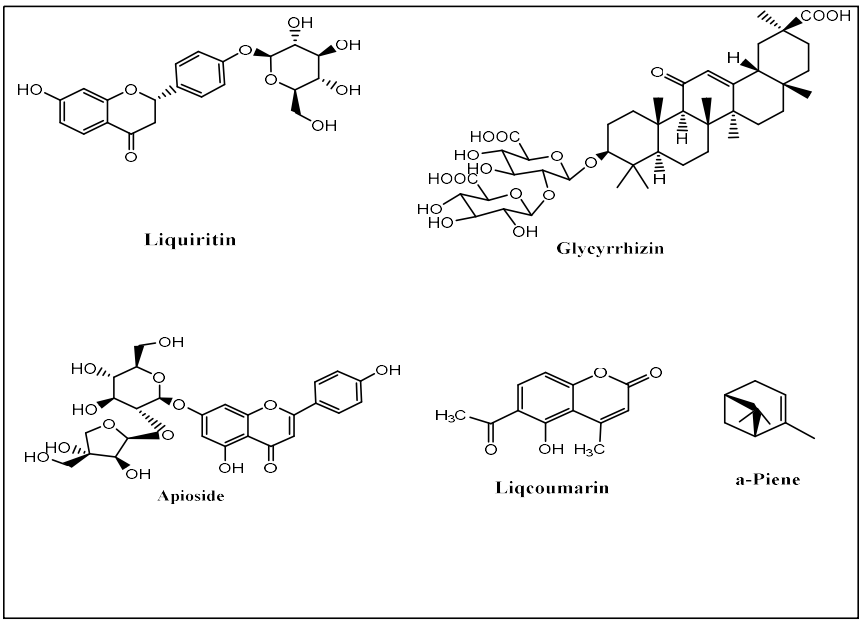

Figure 1: Phytochemical Constituents of *Glycyrrhiza glabra*

Coumarins:

Analogues of coumarins like liqcoumarin, glabrocoumarone A and B, herniarin, umbelliferone, and glycyrin were identified and isolated by Williamson **[19]**. Kinoshita *et al*., reported coumarinic derivatives from *Glycyrrhiza glabra* viz., liqcoumarin, glabrocoumarone A and B, herniarin, umbelliferone, glycocoumarin, licofuranocoumarin, licopyranocoumarin and glabrocoumarin **[20]**.

Essential oils and other compounds:

Several fatty acids, phenol, guaiacol, asparagines, glucose, sucrose, starch, polysaccharides, and sterols were isolated by Näf and co-workers **[31]**. The components like α-pinene, β-pinene, octanol, γ-terpinene, stragole, isofenchon, β-caryophyllene, citronellyl acetate, caryophyllene oxide, and geranylhexanolate are present. The phytoestrogens isolated from the roots of *G. glabra* showed the presence of daidzein, daidzin, genistin, ononin, glycitein, genistein, and coumestrol **[32]**.

TRADITIONAL USES *GLYCYRRHIZA GLABRA* LINN.:

Glycyrrhiza species exhibit several medicinal applications against several diseases like hypocholesterolemia **[33]**, anxiety **[34]**, microbial infections **[35]**, Alzheimer's disease **[36]**, ulcers **[37]**, cancer **[38]**, diabetics **[24]** and hepatoprotective activities **[39]**. It also exhibits activities like anti-allergic **[40]**, antioxidant **[41]**, anti-inflammatory **[42]** and skin eczema **[43]**. The various components of essential oil extracts from the *G. glabra* such as saponins, flavonoids, phenolics, etc are acknowledged for their efficient antimicrobial activities **[43-47]**. Various pharmacological studies revealed that *G. glabra* has been potentially used for the treatment of diseases like AIDS chronic hepatitis B and C **[48-51]**.

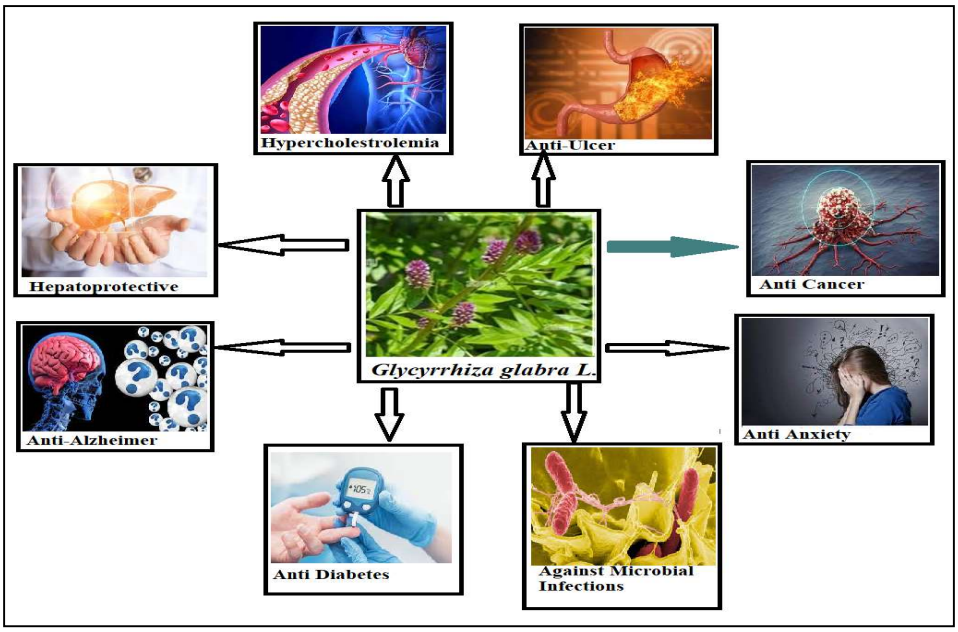

Figure 2: Traditional uses of *Glyccyrhiza glabra* Linn.

The secondary metabolities like glycyrrhizic acid, glabridin, and licochalcone-A can also induce anti-inflammatory activity **[52-55]**. The glycyrrhizic acid and 18β-glycyrrhetinic acid have ability to exhibit potent hepatoprotective activity **[56, 57]**. Glycyrrhizic acid from the essential oil extracts of *G. glabra* can efficiently display protective action in the kidney; also, it can inhibit the genotoxic and nephrotoxic effect caused by administration of cisplatin **[58]**. The traditional uses of *G. glabra* are represented in **Figure 2**.

MECHANISM OF ACTION OF *GLYCYRRHIZA GLABRA* LINN. AGAINST CANCER:

Several cancer cell lines including ovarian cancer cell lines (OVCAR-3 and SK-IV-3) **[59, 60]**, human prostate carcinoma cell lines DU 145 and PC-3 **[61]**, colorectal cancer cell lines (RKO, SW480) **[62]** and breast cancer cell lines (MCF-7) **[63]** show inhibitory actions after the use of *G. glabra* extracts **(Figure 4)**. Compounds like glyasperin A, gancaonin P, licochalcone B, topazolin and gancaonin O derived from this plant exhibit promising cytotoxicity for human oral squamous cancer cell line HSC-2 **[64]**. *In-vitro* analysis of one of the most bioactive constituents; glycyrrhizic acid on the WEHI-3 leukemia cell line revealed the potent anticancer activity via several ways like cell cycle arrest at G_0/G_1 phase, elevating the reactive oxygen species inducing mitochondria negotiated apoptosis. On the basis of these observations Cheuh and co-workers illustrated that the glycyrrhizic acid from the root extracts can efficiently induce antiproliferative activity in the WEHI-3 cell line **[65]**. Glycyrrhizic acid inhibits the mTOR, AKT pathways and STAT3 signalling on the TF-1 cells. It also has ability to reduce the levels of phosphor-Akt and phosphor-mTOR in the concentration dependent manner **[66]**. The human glioblastoma cell line

viz., U251 upon treatment with glycyrrhizic acid for 24 h displays antiproliferative activity with IC_{50} value of 3.67 mM via stimulation of NF-κB negotiated apoptosis **[67]**. The cell viability assay of glycyrrhizin on DU-145 and LNCaP cell lines and the result obtained revealed that glycyrrhizin has ability to induce antiproliferative action in the time and concentration dependent manner **[68]**. The treatment of glycyrrhizic acid can significantly suppress the spread of colorectal cancer tissues towards the liver via the inhibition of 11β-hydrxysteroid dehydrogenase type II in interleukin-13 dependent manner which later on inhibits the manifestation of COX2 and activated Akt **[69]**. The expression and activation of thromboxane synthase is well inhibited in lung carcinoma cell lines after treatment with glycyrrhizic acid. Further analysis related to the selectivity proved that glycyrrhizic acid can efficiently inhibit the cell proliferation in the tumour cells only keeping the healthy cells intact **[70]**.

CONCLUSION:

Overall, many clinical and preclinical studies reflected that the secondary metabolites from the different parts of *Glycyrrhiza glabra* L. are safe clinical interventions for the treatment of cancer. Its wide mechanisms of action against different cancer cell lines are making it an efficient plant based pharmacological scaffold for the treatment of cancer.

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