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Exploration of Heterocyclic Compounds in Cancer Therapeutics

Vishal Vats [1], Kunal [1], Anju Dhiman [1], Etash Vashist [1], Rohit Kumar [2], Sandeep Dhiman [3],
Chhavi Singla [4]

[1] Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak-124001, Haryana, India

[2] Department of Pharmaceutical Engineering and Technology, 11T BHU, Varanasi, Uttar Pradesh-221005

[3] Kinapse India Scientific Sevices Pvt. Ltd., Gurugram -122001, Haryana, India

[4] Department of Pharmacy, Sushant University Erstwhile Ansal University, Gurugram, Haryana- 122003, India

Corresponding author: Dr. Anju Dhiman
E-mail: aniu.dhiman@ndurohtak.ac.in
Phone: +91-8295951007
Co-corresponding author: Dr. Chhavi Singla E-mail:
chhavisingla@sushantuniversity.edu.in
Phone: +91-9268659221

Abstract: According to World Health Organization (WHO) in 2018, cancer has become the second leading cause of death globally and responsible for an estimated 9.6 million deaths in 2018. Cancer of prostate, lung, colon and urinary bladder are prominently found in men, whereas in women, a significant number of breast, lung, colon, rectum, uterine corpus and thyroid cancer has been diagnosed. Cancer originated due to series of successive mutations in genes and because of these mutations, functions of cells can be altered. Carcinogens play a key role in cancer and gene mutations. Carcinogens like asbestos, nickel, cadmium, radon, vinyl chloride, benzidine, radiations, virus, bacteria, and alcohol causes gene mutations. Due to this reason, there are disturbances in the cell cycle that results in abnormal cellular proliferation.

As far as clinical management is concerned, heterocyclic compounds play a vital role in viral, inflammatory, and fungal diseases including cancer. There are natural drug products with potentially active chemical constituents due to their heterocyclic moieties. For instance, Artemisia absinthium L. (family: Apiaceae)and Ammi visnaga L. (family: Asteraceae) have potential anti-cancer activity. The active chemical constituents of both these plants species have heterocyclic moieties similar to synthetically derived potential anti-cancer drugs and can be considered a better alternative as compared to synthetic chugs in treatment of cancer due to safety at high dose levels.

In the present review, we summarized relevant heterocyclic compounds with anticancer activity present in Artemisia absinthium and Ammi visnaga with their mechanism involved in cancer treatment.

Keywords: Artemisia absinthium L, Ammi visnaga L, cancer, carcinogens, synthetic compounds.

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1. INTRODUCTION

Heterocyclic compounds consists of elements such as nitrogen, oxygen, sulphur other than carbon. In medicinal chemistry, heterocyclic compounds possess considerable biological activity in the treatment of various clinical disorders such as anti-bacterial (Azab et al. 2013), antiviral (Salem et al. 2013), anti-tumor (Chen et al. 2014), anti-inflammatory etc.

Cancer is one of the most fatal health disorders. In terms of mortality rate cancer holds second position after cardiovascular disorders. (Jijja & Dinesh, 2019). Genetic mutation in cells due to mutagens is the root cause of this fatal disorder. Genetic mutation in DNA cause the formation of abnormal cells. These abnormal cells multiply and ignores signaling of cell growth regulations which leads to growth of mast cells. There are numerous potential heterocyclic moieties which are synthesized for targeting cancer by chemist and some of them have been approved by various dilig regulating bodies of world for the treatment of cancer but still there are limitations of marketed drugs (Nandal et al., 2020). Natural products represent the richest source of high chemical diversity and serves as starting points for rational drug design (Dhiman, 2020). Human civilization has used natural sources for maintaining diverse health-related issues since time immortal by traditional healers (Dhiman et al., 2017)(Amrinder and Sharma, 2016). It is reported that ingestion of bioactive compounds reduces risk of many common forms of cancer and harmful diseases like tuberculosis (Garg V et al., 2019). The early symptoms developed can be characterized by dry cough, fever, lethargy and weight loss (Xu et al., 2021). Herbal remedies derived from plants and their products have been used since ancient times (Saini et al. 2020a; Saini et al. 2018) due to their pharmacological activities v.i.z. antioxidant, anti-inflammatory, analgesic, anti-fertility, antimutagenic, larvicidal, anthelmintic activity etc. (Saini et al, 2020b; Dhiman et al., 2017). Several medicinal plants are widely being used in Ayarvedic preparations (Shirwaikar et al. 2007) and contain a large number of secondary plant metabolites, which are of great therapeutic significance (Saini et al., 2016). Flavonoids are the main components of a healthy diet (Dhiman et al. 2016).

Alongwith herbal medicines, nutraceuticals and food supplements are claimed to be beneficial in several disease conditions which include cardiovascular disorder, neurodegenerative disorders, liver disorders, metabolic disorders and cancer prevention (Bansal & Dhiman, 2020) (Jijja et al., 2017) These may be explored for the production of natural medicinal formulations in pharmaceutical dilig industries for several disorders on account of potential antioxidant activity (Bhilana et al., 2018). The clinical significance of plants is because of presence of various potential organic chemical entities. Plants also have natural heterocyclic compounds

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which have potential clinical significance in the treatment of biological disorders (Nandal etal., 2020)

Various anticancer studies have been reported on Ammi visnaga L. and Artemisia absinthium L. Ammi visnaga belongs to family Apiaceae and mainly grows in mediterranean area (Vanachayangkul et al.2009). Artemisia absinthium belongs to family Asteraceae mainly found in moderate area of Asia, North Africa region and in America.

Artemisia absinthium contain heterocyclic constituents named as artemisinin,cischrysanthenyl acetate,quercitin isorhamnetin-3-O-rhamnose glucoside, isoquercitrin, absinthin, Cis-epoxyocimene (Lou SN et al. 2016). Heterocyclicmoities of Ammi vasnaga includes visnagin, pimolin, khellinol, visamminol, khellinin, visandin, cimifugin etc (Winderl et al.2016).

There are numerous synthetic and semisynthetic derivatives synthesized based on the heterocyclic structural moeities present in Ammi visnaga and Artemisia absinthium for cancer and many other biological disorders.

2. ANTICANCER STUDIES OF ARTEMISIA ABSINTHIUML.

Slezakova S. et al., (2017) reported that artemisinin and some of its derivatives like artesunate and dihydro-artemisinin shows anticancer activity. It was also reported that the mechanism of action involved in this is generation of reactive oxygen species, inhibition of cell cycle in GO/GI phase, induction of apoptosis and inhibition of angiogenesis (Slezakova S. et al. 2017). Wong Y.K. et al., (2017) reported that Artemisinin and some of its derivatives were seems to exhibit anticancer activity. It was observed that mechanism of action involved in this is artemisinin-induced changes in multiple signaling pathways, reactive oxygen species production, apoptosis, Ferroptosis-iron-dependent cell death, Autophagy and the lysosomal pathway (Wong Y.K. et al. 2017). Sun X. et al., (2019) reported that artemisinin and its derivative Artesunate shows anticancer activity. It was observed that it shows its action via autophagy regulation (Sun X. et al. 2019). Houh Y. et al., (2017) reported that artemisinin shows anticancer activity. It shows its action by activating Natural killer cells and stimulation of granules exocytosis. The Activation ofNK-92MI cells shows cyto-toxic effect on cancer cells (Houh Y. et al. 2017). Efferth T. et al., (2017) reported that artemisinin and some of its derivatives artesunate, dihydroartemismin, artemether, arteether were seems to exhibit anticancer activity. It shows its effect by artemisinin-induced changes in multiple signaling pathways, reactive oxygen species production, apoptosis, Autophagy, inhibition of angiogenesis and tumor related signal transduction pathways and signal transducers (Efferth

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T. et al, (\2017). Kumar M.S. et al., (2019) reported that artemisinin shows anticancer activity in some cancers like hepatocellular carcmoma, leukemia, colorectal and breast cancer cell lines. It shows its effect by arresting the cell cycle, angiogenesis, regulating signaling in apoptosis, cytotoxicity activity on steroid receptors (Kumar M.S. et al. 2019).

Ren Y. et al., (2016) reported that artesunate, dimethyl amino parthenolide, and L12ADT peptide shows anticancer activity (Ren Y. et al. 2016). Wang J. et al., (2017) reported that artemisinin shows anticancer activity in colorectal cancer cells. It shows its effect on cancerous cells by increasing the production of Heme in cancer cell(Wang J. et al. 2017) Frohlich T. et al., (2017) reported that thymoquinone-artemisinin hybrid shows anticancer activity. They show its potency more than doxorubicin by exhibiting EC50 values of 0.2 11M against the doxorubicin-sensitive as well as the multidrug-resistant leukemia cellsFrohlich T. et al. 2017). Frohlich T. et al., (2016) reported that artemisinin and its derivative dihydroartemisinin, artesunic acid and artemether shows anticancer activity (Frohlich T. et al. 2016). Das A.K. et al., (2015) reported that artemisinin shows anticancer activity via the mechanism followed by artemisinin-induced changes in multiple signaling pathways, arrest of cell cycle at Go Gl, reactive oxygen species production, apoptosis, autophagy, inhibition of angiogenesis, tumor related signal transduction pathways and signal transducers Das A.K. et al. 2015).

Li Z. et al., (2016) reported that artemisinin and its derivative are capable of generation of toxic free radicals through endoperoxide moiety, arresting of cell cycle, apoptosis induction, tumor angiogenesis inhibition thus show anti-cancer activity (Li Z. et al.2016). Yao Y. et al., (2019) reported that artemisinin and its derivatives artemether (ARM), artesunate (ARS) and dihydro artemisinin (DHA) are capable of inhibition of cancer of breast in females. The process involved in this is that they suppress TGF-ß signaling an thus activation of L-929CAFs and CAFs is inhibited, and which lead to decreased interaction between tumor and tumor microenvironment (Yao Y. et al. 2019).

Chen J. et al., (2018) reported that artemisinin might be capable of inhibition of c6 cells proliferation and cause arrest of cell cycle and apoptosis of caspase-3-dependent cell and therefore, shows anticancer activity in rat model (Chen J. et al. 2018). Zhou Y. et al., (2016) reported that artemisinin was capable of exhibiting anti cancer activity and act by reduction of hemin to heme via protein thiols, necessary for activation of endperoxide and subsequent protein alkylation (Zhou Y. et al. 2016). Wang Y. et al., (2019) reported that artemisinin derivatives are capable of reversing the P-gp mediated multi dilig resistance and are used for the purpose of designing the rational artemisinin-based combination therapies against cancer (Wang Y. et al. 2019).It was reported that dihydro-artemisinin can be used as anticancer compound. HSPA5 can be capable of behaving as a negative regulator of DHA-induced

ferroptosis. Thus by inhibiting the negative feedback pathway, it may cause strengthening of therapeutic effect (anti-glioma activity). Nosrati H. et al., (2019) examined artemisinin cell cultures on human breast cancer cells and observed that significant MCF-7 cells inhibition was caused by biotin-PEG-PCL nanoparticles and does not effect HFF2 cells, therefore, show anticancer effect (Nosrati H. et al. 2019).

Zhu S. et al., (2020) reported thatartemisinin is capable of showing anti-cancer activity. It was observed that artemisinin-induced ferroptosis can be used to treat cancer(Zhu S. et al. 2020). Yao Z. et al., (2018) observed that dihydroartemisinin taken with 5-FU may promote the activity of 5-FU via ROS-mediated apoptosis and alters the BCL-2/BAX expression ratio. Therefore, dihydroartemisinin can be used as an anticancer agent (Yao Z. et al. 2018). Lam N.S. et al., (2019) reported that artemisinin, and its derivative dihydroartemisinin, shows anticancer activity. They also reported that it shows its action by inhibition of cancer cell proliferation, apoptosis, metastasis inhibition, inhibition of angiogenesis and tumor related signal transduction pathways and signal transducers (Lam N.S. et al. 2019).

Roh JL. et al., (2017) reported that artesunate exhibit anticancer activity. It shows its effect by inducing an iron-dependent and ROS-accumulated ferroptosis (Roh JL. et al. 2017). Yoshida G.J. et al., (2017) reported that artemisinin is responsible for inhibition of autophagy regulation that will lead to cell death, and ultimately treat cancer (Yoshida G.J. et al. 2017). Augustin Y. et al., (2015) reported that artesunate shows anticancer activity. They observed that it shows its effect by inhibition of angiogenesis and immunity enhancement (Augustin Y. et al. 2015). Steely A.M. et al., (2017) reported that artemisinin can be used as a potential anticancer dilig for prostate cancer. It has been observed that artemisinin initiates ubiquitin26S proteasome-mediated degradation of AR (androgen receptor) protein without altering receptor transcript levels and helps in treating cancer(Steely A.M. et al. 2017).

Yan X. et al., (2015) also reported that artemisinin exhibits anticancer activity. In their research study, they observed that artemisinin shows anticancer activity due to the presence of endoperoxide moiety which is activated by cellular ion (Yan X. et al. 2015). Gharib A. et al., (2015) reported that artemisinin and transferrin-loaded magnetic nanoliposomes combination exhibits anticancer activity. It has been reported that combination of artemisinin and transferrin-loaded magnetic nanoliposomes may initiate the process of apoptosis m the mice against breast cancer cell lines and capable of reducing the volume of tumor in mice after 15 days of treatment (Gharib A. et al. 2015). Gruber L. et al., (2018) reported that artesunic acid and derivatives of artesunic acid shows anticancer activity by inducing DNA breakage which

ultimately causes cell death. It has been reported that artesunic acid is responsible for apoptosis of cancer cells by production of reactive oxygen species via iron (Glilber L. et al. 2018).

Li Y. et al., (2020) reported that artemisinin and its derivative are capable of inhibitibg cell proliferation, induce cell cycle arrest and cell death by apoptosis of cancer cells thus show anti cancer activity (Li Y. et al. 2020). Li X. et al., (2016) reported that artemisininmelphalan conjugate is capable of showing cytotoxicity to cancer cell in the ovarian cancer. This will cause inhibition of growth and proliferation of cancer cell in the female ovary and will lead to s-phase arrest, apoptosis (Li X. et al. 2016).

Zhang J. et al., (2018) reported that artemisinin shows anticancer activity by enhancing cytoprotective mitophagy induced by artemisinin via PINKI -dependent pathway (Zhang J. et al. 2018). Liu Y. et al., (2018) reported that dihydroartemisinin (DHA) shows anticancer activity as it was capable of inhibiting proliferation, migration, and invasion of ovarian cancer cells, and also capable of inducing apoptosis in vivo(Liu Y. et al. 2018). Zou J. et al., (2019) reported that dihydroartemisinin (DHA) can be capable of showing anticancer activity. Zheng L. et al., (2018) reported that artesunate was found to be able of inducing apoptosis, reduction of migration and invasion of uveal melanoma cells (Zheng L. et al.
2018).

Wei S. et al., (2019) reported that artesunate can be capable of inhibiting glioma cell growth and invasion. Thus, artesunate exhibits anticancer activity (Wei S. et al. 2019). Paccez J. D. et al., (2019) reported that dihydroartemisinin blocks Axl expression leading to apoptosis, decrease in cellmigration, cell proliferation, prostate tumor development. Thus, dihydroartemisininexhibits anticancer activity (Paccez J. D. et al. 2019). Jiang F. et al., (2018) reported that artesunate (ART) was able to induce the apoptosis of HCTI 16 cells both in vitro and in vivo, thus inhibit proliferation of cancer cell growth. Thus, artesunate exhibit anticancer activity (Jiang F. et al. 2018). Liu X. et al., (2018) reported that dihydroartemisinin (DHA) was capable of causing induction of autophagic cell death (Liu X. et al.,2018). Li Y. et al., (2019) reported that artemisinin was capable of regulation of HCC cell growth, migration, and invasion thereby exhibits anticancer activity (Li Y. et al. 2019).

Tsuda K. et al., (2018)reported that artesunate shows anticancer activity through inhibition of angiogenesis, induction of apoptosis, generation of reactive oxygen species, and also inhibit the activation of hypoxia-inducible factor-la (HIF-lff) (Tsuda K. et al. 2018). Shanmugam
M.K. et al., (2017) reported that artemisinin can be used as a potent anticancer agent for the treatment of different type of cancers (Shanmugam M.K. et al. 2017). Jamalzadeh L. et al., (2017) reported that artesunate shows anticancer activity. They observed that intrinsic and

extrinsic caspase-dependent pathways are responsible for induction of apoptosis which lead to inhibition of growth of MCF-7 breast cancer cells (Jamalzadeh L. et al. 2017).

Alven S. et al., (2020) reported that different nanoparticle formulations of artemisinin and its derivatives can also be used in the treatment of cancer (Alven S. et al. 2020). Chen J. et al., (2015) reported that artemisinin can be used as a potent anticancer agent for the treatment of different types of cancers. In this study, it has been reported that breakdown of artemisinin bridge by Mn^2+ may lead to death of cancer cells (Chen J. et al. 2015).

Yu H. et al., (2018)rep01ted that coumarin-dihydro artemisinin hybrids are capable of showing anticancer activity. It was observed that they causes inhibition of proliferation of HT-29 cell lines, migration of tumor cells, arresting of GO/GI phase of HT-29 cells and also by apoptosis of cancer cells (Yu H. et al. 2018). Greenshields AL. et al., (2016) reported thatartesunate can be used as a potent anticancer agent for the treatment of different types of cancers. It is reported that artesunate shows its effect by ROS dependent damage of DNA as well as cell death (Greenshields AL. et al. 2016).

Zhang Y. et al., (2018)reported that artemisinin can be used as a potent anticancer agent for the treatment of different type of cancers. It was also reported that the mechanism of action involved in this is generation of reactive oxygen species, inhibition of cell cycle in GO/GI phase, induction of apoptosis and inhibition of angiogenesis, prevention of metastasis, and tumor related signal transduction pathways(Zhang Y. et al. 2018). Chen Z. et al., (2019)reported that assembly of mitochondrial targeting nanoparticles (NPs-TPP) as artemisinin-N,N '- bis(octadecyl) - L - glutamic diamide (ARTLGC12) prodrag can be used as a potent anticancer agent for the treatment of different type of cancers. It shows its effect by generating reactive oxygen species and killing cancerous cells Chen Z. et al. 2019).

Tran T.H. et al., (2016)reported thatartesunate-loaded nanostructured lipid carriers (ARTNLCs) can be used as a potent anticancer agent for the treatment of different type of cancers.

In his study they observed that can be capable of inducing apoptosis in MCF-7 as well as MDA-MB-23 Icells at higher rate than the free artesunate (Tran T.H. et al. 2016). Yang Y. et al., (2019)reported thatArtesunate can be capable of inhibiting the retinoblastoma tumor growth, induces tumor cell apoptosis and upregulates KLF6 expression. Thus, show anticancer activity (Yang Y. et al. 2019). Greenshields AL. et al., (2019)reported thatartesunate (ART) can be used as a potent anticancer agent for the treatment of breast cancers. Artesunate shows its effect through reactive oxygen species (ROS)-dependent G2 M arrest and ROS-independent Gl arrest and thus inhibit breast cancer cell proliferation (Greenshields AL. et al. 2019).

Fröhlich T. et al., (2020) reported that tamoxifen-artemisinin and estrogen-artemisinin hybrids were capable of showing significant anticancer activity. Thus, they can be considered as potent anticancer agent (Fröhlich T. et al. 2020). Zhou C. et al., (2018)reported that dihydroartemisinin is capable of showing anticancer activity by inhibiting the proliferation, induction of apoptosis, and increases cleaved caspase- 3 expression in the CNE- 2Z cells (Zhou C. et al. 2018).

Wu L. et al., (2017) reported that pretreatment of farnesylthiosalicylic acid was capable of sensitizing the Huh-7 and HepG2 cells for artemisinin derivatives (dihydroartemisinin and artesunate) and cause apoptosis of cancer cell via intrinsic and extrinsic pathways (Wu L. et al. 2017). Pasupuleti B.G. et al., (2019)reported that dihydroaltemisinin is capable of showing downregulation of OPN expression, and thus inhibits metastasis of breast cancer cells (Pasupuleti B.G. et al. 2019). Zhang B. et al., (2018)reported thatcarboplatin and dihydroartemisinin combination shows good. anticancer activity on lung adenocarcinoma. They observed that through the activation of p38MAPK dihydroartemisinin is capable of sensitizing the Lewis lung carcinoma cellsto carboplatin therapy (Zhang B. et al. 2018). Mondal A. et al., (2015)reported that artemisinin can be used as a potent anticancer agent for the treatment of cervical cancer. They observed that artemisinin shows apoptotic and antiproliferative action HPV-39-infected ME-180 cells(Mondal A. et al. 2015).

Li N. et al., (2019)reported that dihydroartemisinin can be capable of inhibiting cell proliferation, invasion and metastasis of gastric cancer cell line SGC7901 and induces apoptosis of cancer cell (Li N. et al. 2019). Lu M. et al., (2015)reported that dihydroartemisinin causes inhibition of SERCA activity to release intracellular Ca2 from ER, thus enhance endoplasmic reticulum (ER) stress. Dihydroartemisinin acts as a potent anticancer agent (Lu M. et al. 2015).

Ho H.N. et al., (2017)reported that electrosprayed artesunate-loaded core-shell nanoparticles shows good anticancer activity. Thus, it is used as a potent anticancer agent (Ho H.N. et al. 2017). Tiwari M.K. et al., (2020)reported that Artemisinin can be used as a potent anticancer agent for the treatment of different types of cancer (Tiwari M.K. et al. 2020). Sun C. et al., (2017)reported that ARTa-TPP shows anticancer activity. Thus, it is used as a potent anticancer agent (Sun C. et al. 2017). Gotsbacher M.P. et al., (2019)rep01ted that Artemisinin can be used as a potent anticancer agent for the treatment of different types of cancer (Gotsbacher M.P. et al. 2019).

Xu G. et al., (2016)reported that Dihydroartemisinin can be capable of causing apoptosis in PC3 cells due to less HSP70 expression. Thus, it is used as a potent anticancer agent (Xu G. et

al. 2016).Luo Y. et al., (2018) reported that Dihydroartemisinin (DHA) can be used as a potent anticancer agent for the treatment of different types of cancer (Luo Y. et al. 2018). Chen X. et al., (2017) reported that artesunate (ART) can be used as a potent anticancer agent for the treatment of colorectal cancer. Aftesunate causes the production of Reactive Oxygen species and also causes intrinsic apoptosis of HCT-16 cells, this will occurs due to Suppression of Fatty Acid Synthesis and the NF-KB Pathway (Chen X. et al. 2017). Dong J. et al., (2019)rep01ted that dihydroartemisinin (DHA) can be used as a potent anticancer agent for the treatment of canine mammary tumor. With the help of regulation of expression of EMT-related genes dihydroartemisinin causes inhibition of metastasis and invasion of canine mammary tumor cells (Dong J. et al. 2019).

Chen G. et al., (2016)reported that artemisinin can be used as a potent anticancer agent for the treatment of different types of cancer. They observed that it shows its effect by upregulation ofp21 and p2fl[apl] which lead to arresting of cancer cells at the Gl GO phase (Chen G. et al. 2016). Wang D. et al., (2017) reported that Dihydroartemisinin (DHA) can be used as a potent anticancer agent for the treatment of colon cancer. It shown its effect by targeting the JAK2 STAT3 signaling and thus enhances the apoptosis of colon cancer cells (Wang D. et al. 2017). Sun C. et al., (2015) reported that Artemisinin and its derivative Dihydroartemisinin can be used as a potent anticancer agent for the treatment of cancer. It shows its effect by inhibiting the production of heme and shows mitochondria-dependent cellcidal action, thus used in cancer treatment Sun C. et al. 2015).

Thirusenthilarasan I. et al., (2016) reported that artesunate (ART) is responsible for inhibition of STAT-3 that may lead to the promotion of in vitro apoptosis of cancer cell. Thus, artesunate can be used as a potent anticancer agent (Thirusenthilarasan I. et al. 2016). Li Q. et al., (2015) reported that camptothecin and artesunate (C—Q) conjugate shows anticancer activity by inhibiting the activity against MCF7 breast cancer cells and SMMC-7721 liver cancer cells (Li Q et al. 2015). Liu H. et al., (2017) reported that artemisinin and its derivative dihydroartemisinin can be used as a potent anticancer agent against non-small-cell lung adenocarcinoma A549 cells (Liu H. et al. 2017).

Kim S.H. et al., (2016) reported that transferring enhances the activity of dihydroartemisinin against glioblastoma. Thus, they can be used as a potent anticancer agent (Kim S.H. et al. 2016). Zhang L. et al., (2016) reported that artesunate (ART) shows anticancer activity. It shows its effect by inhibiting the HOTAIR expression, which will lead to decrease in COX-2 expression and this is responsible for its anti-metastatic activity against cervical cancer (Zhang L. et al. 2016). Yang Y. et al., (2019) reported that dihydroartemisinin is responsible for

inhibition of P-gp expression that will lead to sensitization of doxorubicin against Mutant p53 (R248Q)-expressing hepatocellular carcinoma cells (Yang Y. et al. 2019).

Li C. et al., (2019) reported that 13-dihydroartemisinin-emodin (13-DHA-emodin) is capable for inhibition of Ki-67 expression and that will responsible for suppression of proliferation of HepG-2 cells at higher extent and also enhances the apoptotic ratio of HepG-2 cellsLi C. et al., (2019).

Feng X. et al., (2020)reported that artemisinin can be used as a potent anticancer agent for the treatment of different types of cancer (Feng X. et al. 2020). Malami I. et al., (2020)reported that Dihydroartemisinin can be used as a potent anticancer agent for the treatment of different types of cancer (Malami I. et al. 2020). Lian S. et al., (2016) reported that Artesunate (ART) is responsible for causing the changes in biochemical properties of glioma cells, this will results in the inhibition of invasion, migration and proliferation of glioma cells (Lian S. et al. 2016).

Tai X. et al., (2016) reported that combination of dihydroartemisinin and doxorubicin is used as an anticancer dilig therapy. This combination shows its effect by the inhibition of viability of pc-3, OVCAR-3, HeLa, A549, MCF-7 cells. This inhibition of viability of these cells depends upon intrinsic apoptotic pathway that is mediated by caspase-9 and caspase-3 (Tai X. et al. 2016).

llamathi M. et al., (2016) reported that Artesunate (ART) can be considered as a potent anticancer agent. They observed that it shows its effect by causing the apoptosis, antiproliferation, and anti-tumor activity. Thus, it acts as a potent anticancer agent (llamathi M. et al. 2016). Hui H. et al., (2016) reported that Dihydroartemisinin can be capable of suppression of Wnt/ßcatenin signaling and this will results in the suppression of growth of squamous cell carcinoma A431 cells. Thus, it acts as a potent anticancer agent (Hui H. et al. 2016).

Wan X. et al., (2016) reported that Dihydroartemisinin along with Fe-TCPP [(4,4,4,4(porphine-5,10,15,20-tetrayl) tetrakis(benzoic acid)] NMOF (nanoscale MOF) having a CaC03 mineralized coating can be used as a potent anticancer agent (Wan X. et al. 2016). Wang Y. et al., (2019) reported that Dihydroartemisinin and Doxorubicin co-loaded soluplus^{ï} shows potent anticancer activity. Thus, combination is used in treatment of cancer (Wang Y. et al. 2019). Beccafico S. et al., (2019) reported that Artesunate (ART) is responsible for production of ROS and it will also activates p38 MAPK, this will result in apoptosis of embryonal rhabdomyosarcoma cells. Thus, it acts as a potent anticancer agent (Beccafico S. et al. 2019).

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Liu R. et al., (2017) reported that Artemisinin and its derivative (artesunate) is capable of showing mitochondrial mediated cell apoptosis and thus, used as a potent anticancer agent (Liu R. et al. 2017). Dwivedi A. et al., (2019) reported that Artemisone shows potent anticancer activity in melanoma cells. Thus, it is in treatment of cancer (Dwivedi A. et al., 2019). Wang T. et al., (2020) reported that artesunate can be capable of suppression of Wnt/ßcatenin signaling and this will results in the suppression of growth of esophageal cancer EC109 cell. Thus, it acts as a potent anticancer agent. Nguyen HT. et al., (2014) reported that artesunate when loaded into poly-D,L-lactide-co-glycolide (PLGA) nanoparticles then it will enhances its anticancer activity (Nguyen H.T. et al. 2014).

Chen S.S. et al., (2014) reported that p8 is responsible for induction of autophagy and that will lead to enhancement of Dihydroartemisinin induced apoptosis of cancer cells (Chen S.S. et al. 2014). Huang Z. et al., (2016) reported that dihydroartemisinin is responsible for induction of cell cycle Gl arrest(Huang Z. et al. 2016). The structures of some heterocyclic chemical constituents present m Artemisia absinthium L. are given in Figure l .

3. ANTICANCER STUDIES OF AMMI VISNAGA L.

Aydogmus-Ozturk F. et al., (2019) reported that visnagin a compound obtained from Ammi visnaga L. shows anticancer activity against malignant melanoma (HT 144) cell lines. In his research they determined the capacity of visnagin to produce singlet oxygen with the help of RNO bleaching method and MTT assay was used for determination of cytotoxic activity. The Anticancer activity of visnagin (100 gg/mL) against HT 144 cell lines in the standard MTT assay was about 80.93% whereas when the activity was reported in illuminated MTT assay the anticancer activity was found to be 63.19% at similar concentration as taken in standard MTT assay. Thus, in this research he concluded that inhibition of intracellualar oxidative stress via visnagin can be used to inhibit the malignant melanoma proliferation (AydogmusOzturk F. et al. 2019).

It was reported that khellin and visnagm extracted from A. visnaga L. when examined for anticancer activity on four different human cell lines MCF7 (breast cancer cell line), Hep-G2 (liver carcinoma), Hela (cervical carcinoma), I-ICT 116 (colon carcinoma) and found better cytotoxic activity of khellin and visnagm against Hep-G2 cell line. Majid Asadi-Samani et al., (2015) reported that most of the compounds obtained from different herbal plants were found to exhibit anticancer activity and these compounds are ß-sitosterol, curcumin, thymol, kaempferol, 1,8-cineole, vincristine, boswellic acids, cucurbitacin, myrtucommulone, umbelliprenin, quercetin, catechin, taxol, Vinblastine, carvacrol-u-pinene, myrecene (Majid

Asadi-Samani et al. 2015). Koooti W. et al., (2016) reported that Quercetin, Kaempferol, Khellol, Visnadine, Cimitugin, and 13-sitoster are the natural compounds obtained from Ammi visnaga L. were found to show anticancer effect on on T47D cancer cell line, pelvic rhabdomyosarcoma and L20B of mice (Koooti W. et al. 2016).

It wasreported that Khellin and Visnagin isolated from Ammi visnaga L. when examined for anticancer activity on four different human cell lines via SBR assay HCT 116 (colon carcinoma cell lineHep-G2 (liver carcinoma cell line), Hela (cervical carcinoma cell line), and MCF7 (breast carcinoma cell line) and for the purpose of positive control they used Doxorubicin. It was reported that Visnadine, cimifugin, khellol, b-sitosterol, kaempferol, quercetin were found to show anticancer effect by arresting the cell cycle.

Rajni Sharma et al., (2018) reported that ftranochalcone derivative 3g and ftranoflavanone derivative 41 of khellinone shows CYPIAI inhibition at greater level. (Rajni Sharma et al. 2018). The structures of some heterocyclic chemical constituents present in Artemisia visnaga L. are given in Figure 2

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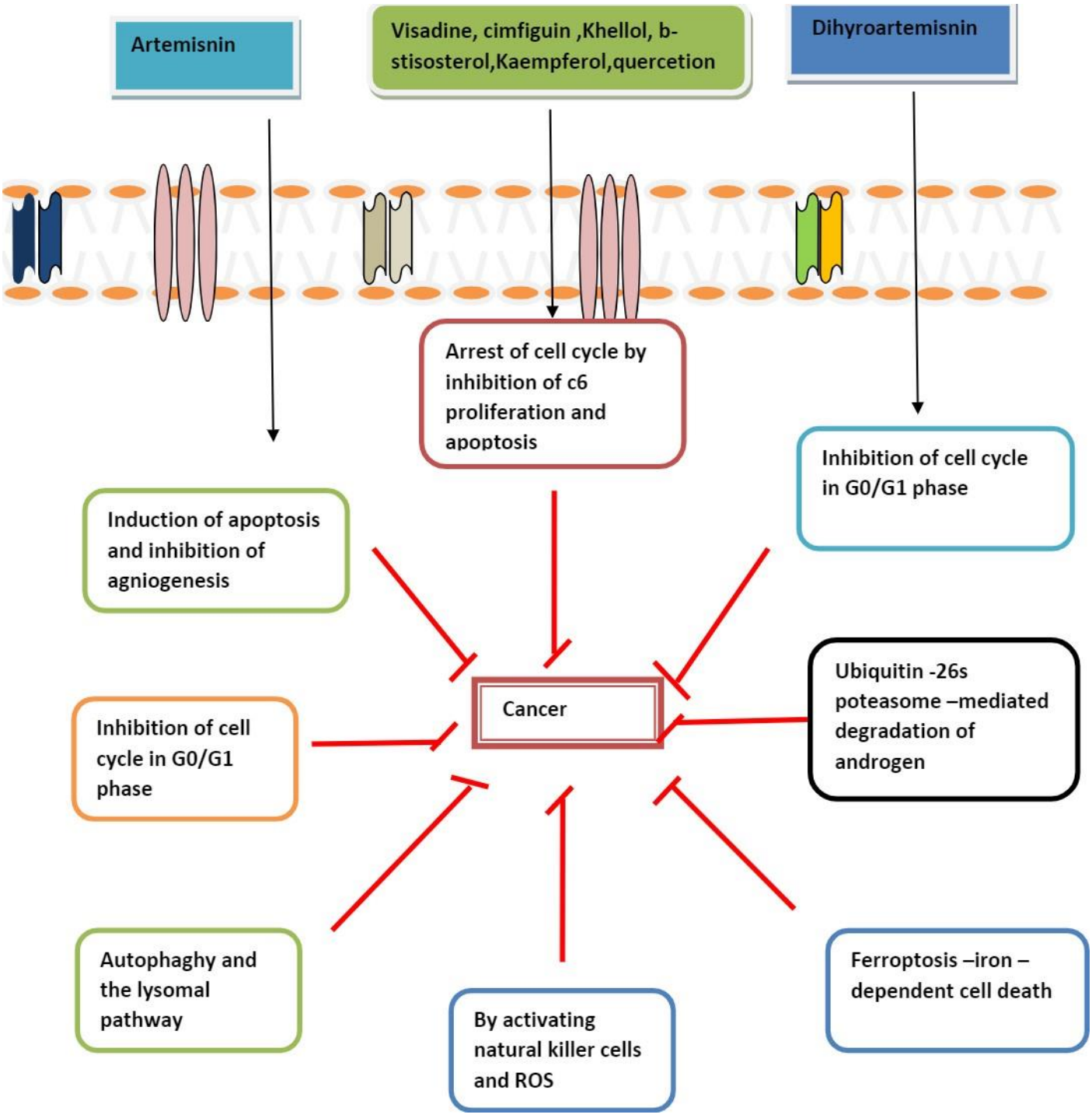

Figure.l. Mechanism of action of Artemisnin, Dihyroartemisnin, Visadine, Cimfiguin ,Khellol, b-stisosterol,Kaempferol,quercetion In treatment of cancer

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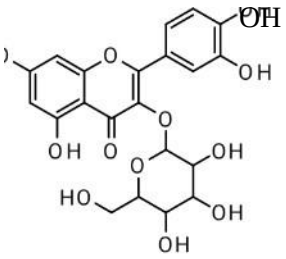

Isoquercitrin

2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-((3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)-4*H*-chromen-4-one

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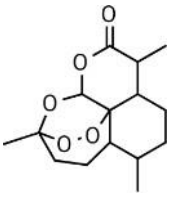
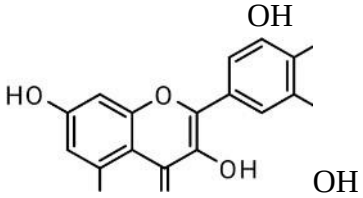


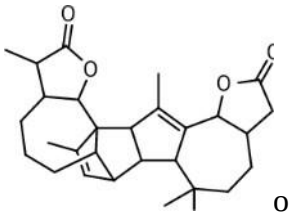


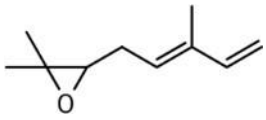
OH O qEcitin

Artefli§nin

3, 6, 9-trimethyloctthydro -3*H*-3,12-epoxy[1,2]dioxepino [4,3-*i*]isochromen-10(12*H*)-one

hydroxy phenyl) -3, 5, 7-tri hydroxy-4Hchromen-4-one



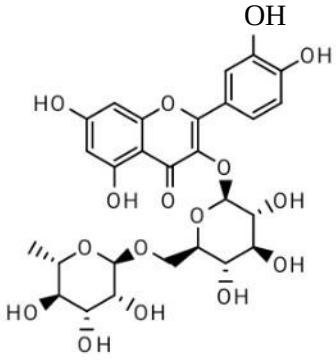


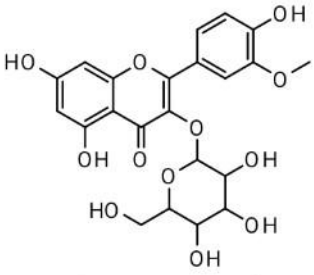
OH

A bS nthi n Cisq)oxyocinpne

(1R,2R,5S,8S,9S,12S,13R,14S,15S,16R,17S,20S,21S,24S)-12,17-dihydroxy-3,8,12,17,21,25-hexamethyl-6,23-dioxaheptacyclo[13.9.2.01,16.02,14.04,13.05,9.020,24]hexacosa-3,25-diene-7,22-dione

(E)-2,2-dimethyl 3-(3-methylpenta24-dian-l-yl)oxirane





Quercitin-3-O-D-glucoside

2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-(((2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-((((2*R*,3*R*,4*R*,5*R*,6*S*)-3,4,5-trihydroxy-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)methyl)tetrahydro-2*H*-pyran-2-yl)oxy)-4*H*-chromen-4-one

Isorhamnetin-3-O-glucoside

5,7-dihydroxy-2-(4-hydroxy-3-methoxyphenyl)-3-((3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)-4*H*-chromen-4-one

Strihydroxy-6

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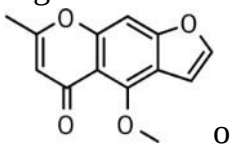
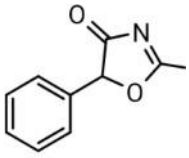
Figure 1. Structures of chemical constituents present in Artemisia absinhthium L.



o o

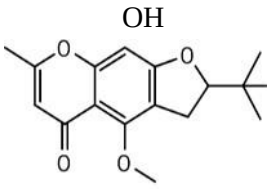
Visnagin

4-methoxy-7-methyl-5H-furo[3,2-g]chromen-5-one



Pimolin

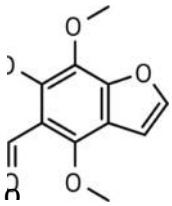
2-aïi nŒ5-phenyl oxazol-4(5H)-one



visamminol

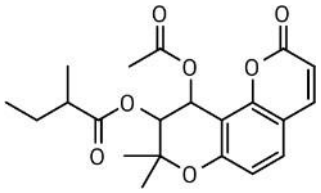
Khellinin

4-methoxy-7-(((3,4,5-trihydroxy-6(hydroxyrœthyl) 6 hydroxy-4,7-dimethoxybenzofuran-5-carbal dehyde

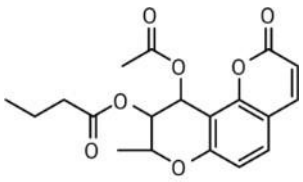


hd linone

2-(2-hydroxypropan-2-yl) -4methoxy-7-methyl-2Hfuro tetrahydro-2H-pyran-2-yl)oxy) [32dthrornen-3(3H)-one flEthyl)-3H-furo[3,2-g]chromen-5-one

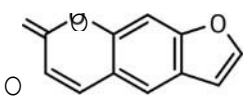


10-æetoxy-8,8-dimethyl-2-oxœ 2, 8, 9, I O-tetrahydropyrano [2, 3- f] chromen-9-yl 2-ÑËthylbutanoate



Dihydrosamidin

V iS1adi n 10-æetoxy-8-methyI -2-oxo-2,8,9,10-tetrahydropyrano[23-f]chrorTHY9-yl butyrate



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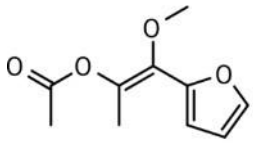
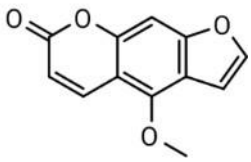


Xanthotoxin



X anthotoxi n

(O- 1-(f uran- 2-yl)
-1-methoxyprop
-1-en-2-yl æetate

B ergapten Psoralen

4 methoxy-7H-f uro
7*H*-furo[3,2-
[3, 2-g] :hromen-7-one g]
chromen-7-one

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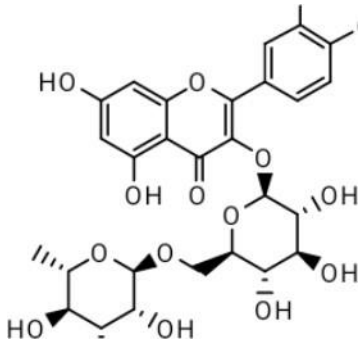
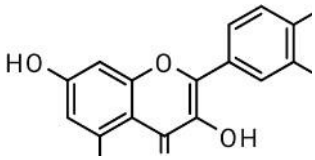


OH
OH

Quercetin-3-O-gluco§de



OH

OHOH

2-(3,4-dihydroxyphenyl)-5,7-dihydroxy

OH O

6- ((((2R3R,4R,

-3-(((2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-

R,4*R*,5*R*,6*S*)-3,4,5-trihydroxy-6-methyltetrahydro

-2H-pyran-2-yl)oxy)methyl)tetrahydro-2*H*

-pyran-2-yl)oxy)methyl)tetrahydro2H

-pyran-2-yl)oxy)-4*H*-chromen-4-one

OH O

Quercetin

2-(3,4-dihydroxyphenyl)

-3,5,7-trihydroxy-4*H*

-chromen-4-one

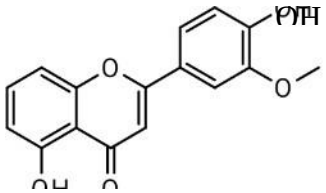
3, 5-di hydroxy-2-

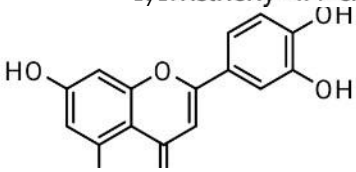
5, 7-di hydroxy-

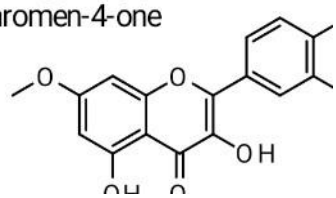
2-

(4-hydroxy-3-methoxyphenyl)

-7-methoxy-4*H*-chromen-4-one







OH O

(4-hydroxyphenyl)

-4H- chromen-4-one

Chrysoeriol

5, 7-di hydroxy-2-

(4 hydroxy-3-methoxyphenyl)

4H- chromen-4-one

Luteolin

2-(3,4-di

hydroxyphenyl)

-5, 7- di hydroxy-

4H-chronvn-4- one

OH

OH

OH O

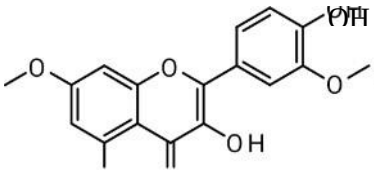
R hamnetin

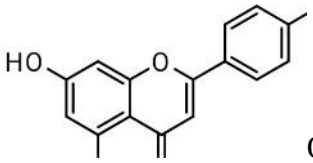
2- (3, 4-di hydroxyphenyl)

-3, 5- dihydroxy-

7methoxy-4H-chrorœn-4-

one





OH

OH O

R hamnazin

OH O

Apigenin

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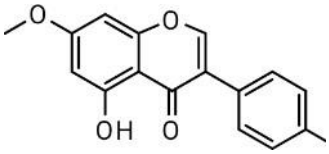
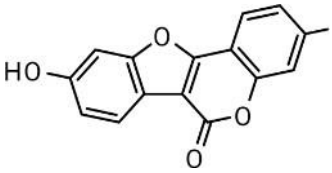


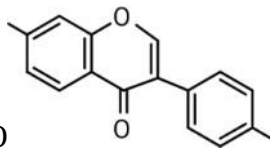
5-hydroxy-3(4-hydroxyphenyl)-7-rrpthoxy-4H-±lrorrpn-4-one

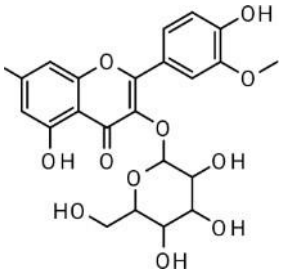
OH

Pruneti n

HO







OH HO

OH

D aidzei n I orhamnetin-3-O-glucoside Coumärol

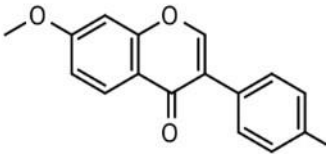
57-dihydroxy-2-(4hydroxy-3

3,9-dihydroxy- 7-hydroxy6H- benzof uro 3-(4-hydroxyphenyl)

-methoxyphenyl)-3-((3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)-4*H*-chromen-4-one

[3, 2-d chrorœn- 6-one -4H- chromen-4-one

Sissotrin



OH

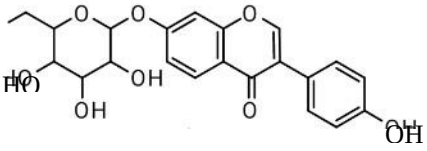
-7-((3,4,5-trihydroxy-6-(hydroxymethyl) Shydroxy-3-(4-methoxyphenyl) I sof

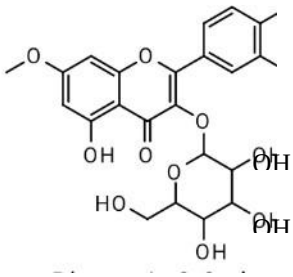
ormononeti n tetrahydro-2H-pyran-2-yl) 3-(4hydroxyphenyl)-7

oxy)-4H-throræ1-4-one -nethoxy-4*H*-chromen-4-one

OH

OH





HO

OH

Daidzin R hametin-3- O-

gl ucoSde

3-(4-hydroxyphenyl)- 2-(3,4dihydroxyphenyl)-5

S tri hydroxy-G -hydroxy- ((3,4 Strihydroxy

(hydroxy methyl) tetråydro- -6 (hydroxymethyl)tetrahydrœ2H-

OH

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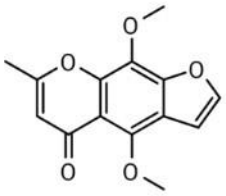
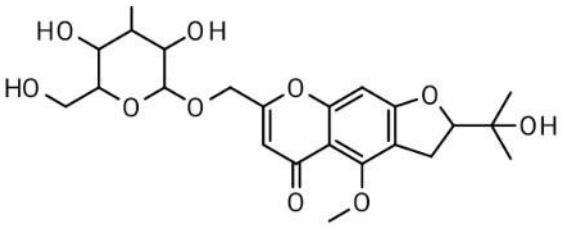


Khellol

-dimethoxy-7-methyl



Prim-O-glucosyl cimifugin

2-(2-hydroxypropan-2-yl)-4-methoxy

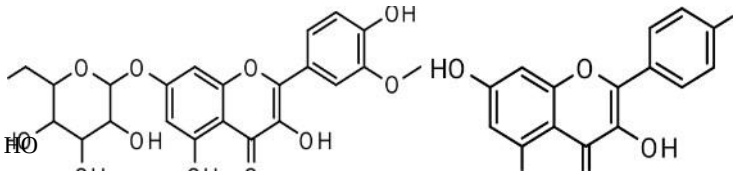
-7-(((3,4,5-trihydroxy-6-(hydroxymethyl)

tetrahydro-2*H*-pyran-2-yl)oxy)methyl)

-2H-furo[3,2-g]chromen-5(3H)-one

4, 9-di

-5H-furo[3, 2-à chromen- Sone



OH

HO

OH OH O OH O

OH

3, 5-di hydroxy-2-(4-hydroxy-

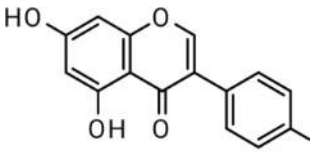
I

3- flPthoxyphenyl)- 7-(345-trihydroxy 3, 5, 7-tri

5-7-di hydroxy-3- hydroxy-2-

(4-hydroxyphenyl) -6-(hydroxymethyl)tetrahydro-2H (4-hydroxyphenyl)

chrorœn-40ne - pyran-2-yl)oxy)- 4H-chromen-40ne - 4H- chromen-4-one



Genistin

OH

sorhametin-7-O-gl ucoSde

Kaenpferol

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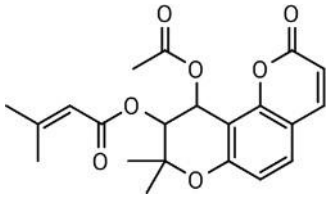
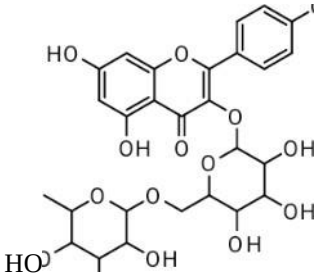


Sam dl n

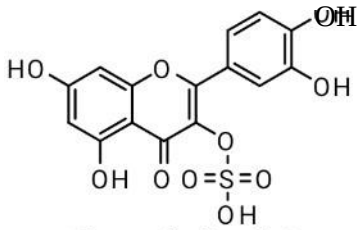
10-acetoxy-8,8-dimethyl o-2,8,9,10-tetrahydropyrano [2,3-f]chromen-9-yl



Kaempf eroI-3-rutinoSde

5,7-dihydroxy-2-(4-hydroxyphenyl)-3-((3,4,5-trihydroxy-6-(((3,4,5-trihydroxy-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)methyl) tetrahydro-2*H*-pyran-2-yl)oxy)-4*H*-chromen-4-one

3-methylbut-2-enoate



Quercetin3-sulfate

2-(3,4-dihydroxyphenyl)-5,7

Rhamnetin-3-sulfate

2-(3,4-dihydroxyphenyl

hydroxyphenyl)

-di hydroxy-4-oxo-4H -chromen-3-yl hydrogen

-3, 5-dihydroxy-7-methoxy -4H-chromen-40ne

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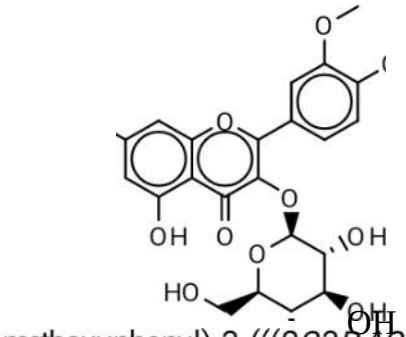
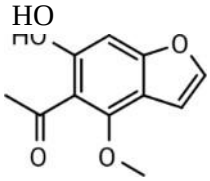


HO oÖ

OH

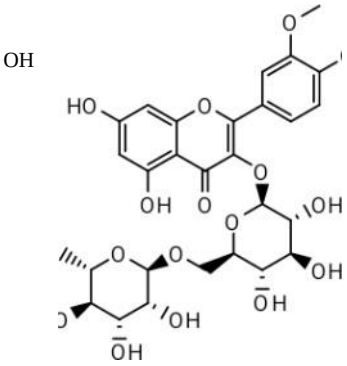
I sorhametin 3-O- ?-d-gl ucoSde

5, 7-di hydroxy-2- (4 hydroxy- 3-methoxyphenyl)-3-(((2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one



V i snagi none

1-(6Hydroxy-4npthoxy-l-balzofuran -5-yl)ethanone

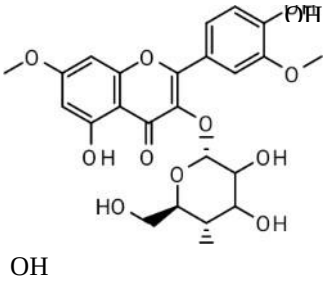


OH

HO

I sorhametin-3-O-rutinoSde

5, 7- dihy dr oxy-2-(4- hy droxy-3- rœthoxy pheny I)

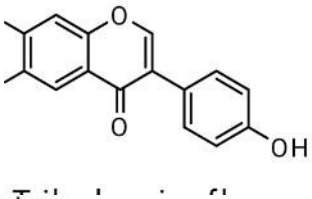


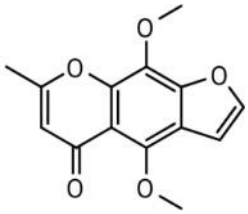
OH

R hamazi n-3-glucoSde

((((2R,3R,4R5R,6$-3,4,5-trihydroxy-6-methyltetrahydro- -pyran-2-yl)oxy)-4H-chromen-4-

5-hydroxy-2-(4hydroxy-3-næthoxyphenyI) one



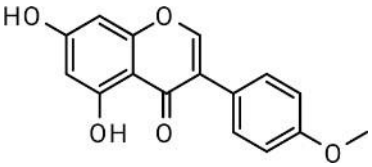


-7-methoxy-3-[(2r,5s,6r)-3,4,5-trihydroxy-6-hydroxymethyl)oxan-2-yl]oxychromen-4-

(hydroxy

3-trihydroxy-6-

one



HO

HO

Biochani n A

4 , 6, 7-Tri hydroxyi so-flavone

Khellin

5, 7-di hydroxy-3- (4- nËhoxypheny l) -4H- chromen-4-one

6,7-di hydroxy-3- (4-hydroxyphenyl) -4H- chromen-4-one

4,9-d ɹmeth -methyl furo[3,2-g] chromen- Sone

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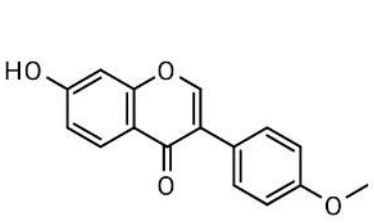
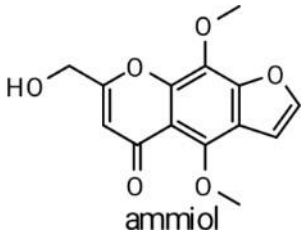


Forrmnonetin 7- hydroxy-3-(4- phenyl) -4H-chroffĐ-4-one



ammiol

7- (hydroxyrnethyl)-4, 97-di nethoxy-5*H*-furo [3,2-g]chromen-5-one

Secondary metabolites present in Ammi visnaga L.

4. CONCLUSION

Since ancient era, plants have been used for the treatment of various disorders. The clinical significance of use of medicinal plant is because of the presence of potentially active chemical constituents. Plants possess many natural heterocyclic compounds having clinical significance in the treatment of cancer. There are numerous synthetic and semisynthetic derivatives that have been synthesized based on the heterocyclic structural moieties of Ammi visnaga L. and Artemisia absinthium L. for the management of cancer and many other biological disorders. Heterocyclic chemical constituents present in Artemisia absinthium such as artemether, arteether, artesunate, dihydroartemisinin, artemisinin and their derivatives shows potential anticancer activity in many scientifically evident research studies. Research studies shows that khellin, visnagin, ß-sitosterol, curcumin, thymol, kaempferol, 1,8-cineole, vincristine, boswellic acids, cucurbitacin, myrtucommulone, umbellipremn, quercetin, catechin, taxol, vinblastine, carvacrol-ff-pinene, myrecene are the heterocyclic compounds present in Ammi visnaga with anticancer activity. Studied conducted on these two medicinal plants shows encouragmg results against cancer studies via different stated mechanisms, and therefore, may be considered as better alternative when compared with available marketed synthetic drugs for cancer treatment due to safety concerns.

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