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Suggested Treatment of Advanced Cancer Patients

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Abstract

More than one million women are diagnosed with breast cancer every year, making it the leading cause of death among women all over the world. It is estimated that one out of every nine Pakistani women will acquire breast cancer, making it the most prevalent type of the disease in the country. The prevalence in Pakistan is two and a half times higher than that in nations such as Iran and India. These include a woman's age and her family's history, an early menarche, combined oestrogen and progestin menopausal hormone intake, alcohol use, inactivity, a low socioeconomic position, and a lack of knowledge about breast cancer. Another risk factor is not having enough information about breast cancer. This review article's objective is to to suggest the advanced treatment for cancer patients . Breast cancer, the disease that affects the most women overall and is a serious concern for public health, strikes one in every eight women in the United States. Immunotherapies that target the specific pathophysiology of breast tumours have recently been developed as a result of recent advances in molecular biology and immunotherapy. Following the start of therapy, it's important to pay attention to the formation of treatment resistance mechanisms, which need to be clarified quickly. In breast cancer targeted therapy, are there any novel molecular resistance mechanisms? And if so, what are the best strategies to overcome this huge obstacle? One of its main goals is to update the public on latest findings in the field, as well as investigate into the possibility of preventing resistance processes in order to lengthen life expectancy for those who suffer from this condition Breast cancer is more likely in women who have certain risk factors. Any relevant risk factors must be evaluated in order to enhance the likelihood of developing an illness. One such risk factor that can be avoided is alcohol consumption. There are, however, some risk factors that cannot be avoided (like a history of breast cancer in the female line of descent). Breast cancer is not a foregone conclusion for women who have risk factors. Breast cancer does not impact all women who have risk factors for the diseas

Introduction

The Greek word "apoptosis" means "dropping off," and it relates to the shedding of bones and tissues. Unlike necrosis, apoptosis describes a cell that actively pursues death in response to particular stimuli. Pathologically and physiologically, apoptosis is a highly selective process. The changes in nucleus and cytoplasm structure caused by programmed cell death are the same in all cell types and species. Apoptosis is distinguished by three primary biochemical changes: the

activation of caspase, the destruction of DNA and proteins, and the recognition of membrane changes by phagocytic cells, which then undergo their own apoptotic process [1, 2]. Research into the process of cell death, also referred to as apoptosis, is an essential component of the study of cell biology. In the context of a medical setting, having an understanding of apoptosis may, in addition to providing insights into the biology of the disease, provide suggestions for treating the apoptotic illness itself. The issue may present itself at any step of the apoptotic process, depending on how far along the process we are. Inactivation of the gene p53, which normally acts as a tumour suppressor, is one example. A wide variety of human cancers have been connected to the deregulation of this gene, which has been shown to increase risk. It has the effect of reducing apoptosis and encouraging the growth and spread of tumours. On the other hand, apoptosis is analogous to a sword with two edges, as the vast majority of scientists are currently engaged in the process of finding new medications that target separate stages of apoptosis. A direct result of this is that apoptosis is a key component in both the development of cancer and the therapy of it. The mechanics of apoptosis, as well as the ways in which abnormalities in the apoptotic pathway delay carcinogenesis and the ways in which apoptosis could be used as a targeted treatment for cancer, are investigated in this article [3]. In some cases, the capacity to undergo apoptosis can be restored or improved, making tumours more susceptible to standard anticancer treatments like chemotherapy and radiation. Apoptosis control in breast cancer is frequently disrupted by genetic mutations, to be overcome, as well as the stratal gene-based techniques that have been tested [4]. Tumour cells rely solely on these systems and components for survival, and hence are more susceptible to apoptotic activation than normal tissues [4-6]. In the lack of recent advances in molecular genetics that have created the framework for the creation of tailored therapeutic approaches, effective molecular treatments for breast cancer remain limited. The lack of effective treatments for breast cancer necessitates the development of new ones. One of these is gene therapy, which aims to treat genetic disorders [7]. Newer, more effective drugs that can target breast cancer cells while preserving healthy cells are available in addition to chemotherapy and hormone treatment. Currently, these personalised techniques are used in conjunction with traditional treatment. Customized medications, on the other hand, usually have less adverse effects than regular chemotherapy treatments. Targeted therapy for breast cancer makes use of medications that specifically halt the growth of cancerous cells in the breast. Breast cancer cells are stimulated to develop by abnormal proteins (such as HER2), which can be reduced or eliminated through targeted therapy. Targeted therapies for breast cancer are chemicals or medications that interfere with the action of certain molecules that are important for tumour cell proliferation and survival. Some receptors, when activated, can trigger genes important for cancer cell proliferation and growth in breast cancer cells. Both ER+ and PR+ breast cancers have hormone receptors, such as oestrogen or progesterone, and are the two types of breast cancer (or both). The oestrogen receptor (ER) is expressed in the majority of breast cancers, accounting for 75% of all breast cancers. Postmenopausal women are more prone to get the condition, which has a 98 percent 10-year survival rate. This type of breast cancer has lower tumour grade, less HER2 oncogene amplified tumours, and fewer p53 tumour suppressor gene amplifications and PR expression, Additionally, there are fewer soft tissue and bone metastases and fewer relapses. Additionally to ER expression, multigene testing can be utilised for evaluating treatment recommendations for hormone-positive breast cancer, Patients who might benefit the most from adjuvant chemotherapy that includes hormone therapy can be identified this way. In breast cancer cells, there is typically an overexpression of members of the epidermal growth factor (EGFR) family of receptor tyrosine kinases (RTKs). Approximately forty percent and twenty-five percent of all breast cancer patients, respectively, are found to have an overexpression of EGFR and HER2. RTKs belonging to the family of the epidermal growth factor (EGFR) are generally overexpressed in breast cancer cells.

Around forty and twenty-five percent of all breast tumours, respectively, have been associated to overexpression of EGFR and HER2, which has been connected to aggressiveness and a poor prognosis in these cases. It is generally accepted that tumours are the cause of both aggressive tumour behaviour and a bad prognosis. When it comes to TNBC, there is no oestrogen, no progesterone, and no HER2. Unfortunately, there is now no treatment available for this particular form of breast cancer; as a result, the prognosis is not good. Even while some genetic abnormalities and epigenetic changes in molecular pathways have been found, many other types of pathway blockades must be used together for therapeutic objectives.. Alternative proliferative pathways are used by subtypes of breast cancer such as TNBCs, which are still poorly known and require rapid attention and explanation. Compensatory pathways that lead to resistance mechanisms may have been better understood because to the combination therapy and discovery of new breast cancer target molecules.

Objective

The objective of this study is to suggest the advanced treatment for cancer patients

Through the Bcl-2/Bax Pathway, Anticancer TCMs

The process of intrinsic apoptosis takes place inside of a cell when the mitochondria contain both Bcl-2/Bax and Bax. This is due to the Bcl-2 protein's capacity to block Cyt-migration c's from the cytosol to the mitochondria. The amount of apoptosis that can take place as a consequence of this is restricted. In cells, Bax functions as an apoptosis promoter, in contrast to Bcl-2, which performs the role of an apoptosis repressor. The Bcl-2 family, which helps ensure the survival of cells, is comprised of the proteins Bcl-2, bcl-xL, Bax, and maybe BOK (BH) [8]. This family of Bcl-2 proteins regulates the release of apoptogenic substances from mitochondria by controlling the outer membrane of the mitochondrial outer membrane (MOM). Controlling the MOM's integrity thus mediates the majority of cytotoxic treatment responses. Bcl-xL, an anti-apoptotic protein, has been demonstrated to increase melanoma cell chemo resistance and decreasing it lowered treatment resistance[9]. The equilibrium and ratio of Bcl-2/Bax within a cell are what decide whether or not that cell will die. [pagebreak] Through the use of traditional Chinese medicine, it has been established that restoring harmony to the Bcl-2 family and/or altering the Bcl-2/Bax ratio might hasten the death of cancer cells (TCM). In this article, we will discuss Hedyotis diffusa Willd and Gambogic acid in addition to Prunella vulgaris (PV), hyperside, Rabdosiarubescens (RR), Ordonin, and Solamargine (SM). In addition, we will discuss extracts from the plants Solanum lyratumThunb and Huaier. PV is widely utilised in traditional Chinese medicine due to its potential to inhibit cancer cell proliferation and induce apoptosis in cancer cells (TCM). PV was able to eliminate thyroid cancer cells after changing the Bcl-2/Bax ratio and activating caspase-3. A combination of PV and a taxane may benefit breast cancer patients by increasing anticancer effectiveness while reducing taxane-induced toxicity, hence slowing the progression of the disease. The main active pharmacological component of PV, hyperoside, induces apoptosis while also inhibiting proliferation in A549 lung cancer cells. [10]. RR, a medicinal herb plant, contains anti-inflammatory, antibacterial, anticancer, and neuroprotective properties, among other biological and pharmacological effects. According to the findings of this investigation, RR was able to inhibit cell proliferation in MDA-MB231 breast cancer cells and cause them to undergo apoptosis. Cancer patients in China benefit from the use of RR and its extracts, which alleviate symptoms, reduce tumour burden, slow disease progression, and lengthen survival time. These include malignancies of the stomach, esophageal lining, gastric lining, liver, and breast, to name a few. In human breast cancer, Reducing multidrug resistance may be possible by using chloroform and/or ethyl acetate extracts (MDR). The MCF-7/Adr cancer cells [11]. Notable are the anticancer activities of RR

diterpenoid extract Oridonin. Stomach, breast, and colon cancer cells' apoptosis was greatly boosted by oridonin treatment. Human gastric cancer SGC-790 cells decreased cell proliferation and increased apoptosis when the Bcl-2/Bax ratio was altered. In MHCC97-H liver cancer cells, 12.5–100 M oridonin was found to have an effect on the death of cancer cells, and this was linked to a decrease in Bcl-2/Bax ratio and an increase in caspase-3, -9, and Cyt-c activity (Zhu et al., 2013). Additionally, it was shown that oridonin reduces the mRNA for Bcl-2 and increases the mRNA for Bax in mitochondria, both of which are associated with lower cell growth and higher mortality in cancer cells such as HeLa, SGC996, and NOZ [12]. For its part, the Mdm2 inhibitor Oridonin boosted Nutlin-3's cytotoxicity against wild-type p53 osteosarcoma U2OS cells by raising Bim levels and lowering those of Bcl-2 and Bcl-x. Oridonin lowered Bcl2 expression while elevating Bax in ovarian, pancreatic, and liver cancer cell lines, rendering numerous anticancer drugs ineffective [13] The evergreen and perennial Solanum incanum is a member of the family Solanaceae. Because of its ability to alleviate pain, incanum is a well-known traditional Chinese medicine (TCM) plant in China. In liver cancer SMMC7721 and HepG2 cells, it was found that SM caused apoptosis, G2/M cell cycle arrest, and DNA damage. This was accomplished by lowering Bcl-2 levels while simultaneously increasing Bax and caspases-3 and -9 activity. According to the findings of one study, the levels of Bax and Bcl-2 in human cholangiocarcinoma QBC939 cells were respectively elevated and lowered by SM therapy [14]. According to findings from earlier research, SM inhibits the growth of malignant WM115 and WM239 melanoma cells more effectively than it does the growth of benign WM35 cells, with the latter group suffering only minimal damage. Bcl-2 and Bax, as well as caspases-3 and 9, are associated with alkaloid glycoside. It has been demonstrated that the alkaloid glycoside can increase the therapeutic efficacy of chemotherapeutic medicines such as cisplatin, epirubicin, and trastuzumab in the treatment of breast cancer. SM have been found to be reduced in human breast cancer cells. According to the findings of one study, the levels of Bax protein were increased by SM in human cholangiocarcinoma QBC939 cells, but Bcl-2 levels were decreased. cells that are afflicted with malignancy [15]. As a result, SM could be utilised in concert with existing cancer treatments as a novel cancer therapy. The Solanaceae family includes the medicinal plant Solanum lyratumThunb. HedrbaSolinaLyrati, or LyratumThunb, is a well-known TCM herb for treating allergies and boosting the immune system. Cell proliferation and apoptosis in murine leukaemia are examined lyratumThunb extract significantly inhibited WEHI-3 cells, as well as having substantial anticancer potential against allografted tumours derived from WEHI-3 leukaemia cells. So. lyratumThunnb ethanol extract has been shown to increase cytotoxicity and induce apoptosis in osteosarcoma U-2 OS cells by lowering Bcl-2 levels and boosting Bax levels. Saponins isolated from Sophora lyratumThunb enhanced apoptosis in human cervical cancer Hela cells by decreasing Bcl-2 expression and raising Bax expression. [16]. Moreover, in mice with Lewis lung cancer and S180 sarcoma, researchers discovered, the So. lyratumThunb extract showed strong anticancer action and enhanced survival[17]. Since around 1,600 years ago, Traditional Chinese Medicine in China has made use of the fungus TrametesrobiniophilaMurr. (huaier) for the purpose of "balancing and healing diarrhoea." It was determined through research that T. robiniophilaMurr possessed both anti-angiogenic and anticancer activities. The research was conducted on the bacterium. T. robiniophila Murr. aqueous extract inhibits tumour cell proliferation and induces cell death in human lung cancer A549, renal carcinoma 786-O, and prostate cancer PC3 cells. This is accomplished through the suppression of the anti-apoptotic Bcl-2 protein and the enhancement of the pro-apoptotic Bax protein and the apoptosis pathway [18]. Therapeutically, paclitaxel, cisplatin, and T. robiniophilaMurr may be considerably improved by the addition of T. robiniophilaMurr, and rapamycin are some of the most often used therapeutic drugs, as well as animal models of

cancer xenografts. Additionally, it is probable that cancer cells caused by T. robiniophilaMurr. are more susceptible to the damaging effects of radiation caused by radiation. [19].

Traditional Chinese Medicine (TCM) practitioners in China use the herb H. diffusa Willd, which is a member of the Rubiaceae family, to treat flu-like symptoms as well as asthma, jaundice, impure blood, urinary tract infections, acute appendicitis, biliousness, and some types of cancer that affect the digestive tract. The member of this family known as H. diffusa Willd is a good example of a well-known member of this family. This technology has a significant impact on the cancer treatment drug research and development being carried out in China. Willd was responsible for the death of Dispersion of H. diffusa RPMI 8226 myeloma cells. This procedure resulted in a considerable drop in the levels of Bcl-2/IL-6/VEGF mRNA. Ovarian cancer A2780 cells had their proliferation and mortality considerably stifled when exposed to H. diffusaWilld, which worked by inhibiting Bcl-2 and increasing the creation of caspases-9 and-3 [20]. In order to induce apoptosis in HT-29 colon cancer cells, an ethanol extract of H. diffusa Willd must be administered at concentrations ranging from 0.25 mg/ml to 5 mg/ml. Altering the ratio of Bcl-2 to Bax and activating caspases 3 and 9 are two potential methods for achieving this goal within the mitochondrial-mediated cell death pathway. The growth of colorectal cancer SW620 cells was found to be effectively inhibited by a chloroform extract of H. diffusaWilld, which also caused the cells to commit suicide. Increasing the expression of Bcl-2-X while simultaneously reducing the expression of Bcl-2 and survivin is one way to accomplish this goal. Both HCT-8 and HepG2 cancer cells had their drug resistance altered as a result of the interaction between H. diffusaWild and 5-fluorourical. In order to do this, Bcl-2 expression was brought down, whereas Bax expression was brought up [21]. Clinical investigations have indicated that mixing H. diffusaWilld with chemotherapy drugs can lessen drug-induced side effects and encourage greater life expectancy for patients with advanced liver or esophageal cancer [22]. Evergreen Garcinia hanburyi (Clusiaceae), also referred to as gamboge, is a species of the Clusiaceae family. Since ancient times, Traditional Chinese Medicine (TCM) practitioners have relied on to rid the body of toxins, control parasites, and stop bleeding. Gambogic acid, the principal active component of gamboge, has been proven to have a significant effect on a wide variety of human cancer cells and tumours. This effect can be seen across a number of different types of cancer. In addition to lung and breast cancers, the United States also has a significant problem with leukaemia and lymphoma, as well as a number of subtypes of each of these malignancies. Gamboge was used in the extraction of gambogic acid [23]. Human colorectal, breast, gastric, esophageal and leukaemia cells may be more susceptible to cytotoxicity and death when coupled with 5-fluorouracil, doxorubicin, oxaliplatin and proteasomal inhibitors such as gambogic acid (MG132 or MG262) [24]. A prior study on cancer patients found that 14.29% of them experienced clinical remission after taking gambogic acid; the benefit rate was 76.19%. Carpesium varicatum is a traditional Chinese medicine that is used to cure a wide variety of ailments, including snakebites, bruising, fever, and clotting. It has been shown to possess hemostatic, anti-inflammatory, analgesic, vermifuge, and detoxifying effects. C. divaricatum was used to separate and extract telekin, which significantly reduced the growth of a wide variety of cancer cells. This was done in order to treat cancer. On HepG2 cells generated from liver cancer, Telekin inhibits cell growth by activating caspases 9 and 3, and caspases 9 and 3 are then released. This results in a reduction in Bcl-2 and Apaf-1 levels, as well as an increase in Bax expression [25]. Telekin has been proven in several studies to be cytotoxic to cancer cells and to be able to cause apoptosis in these cells.

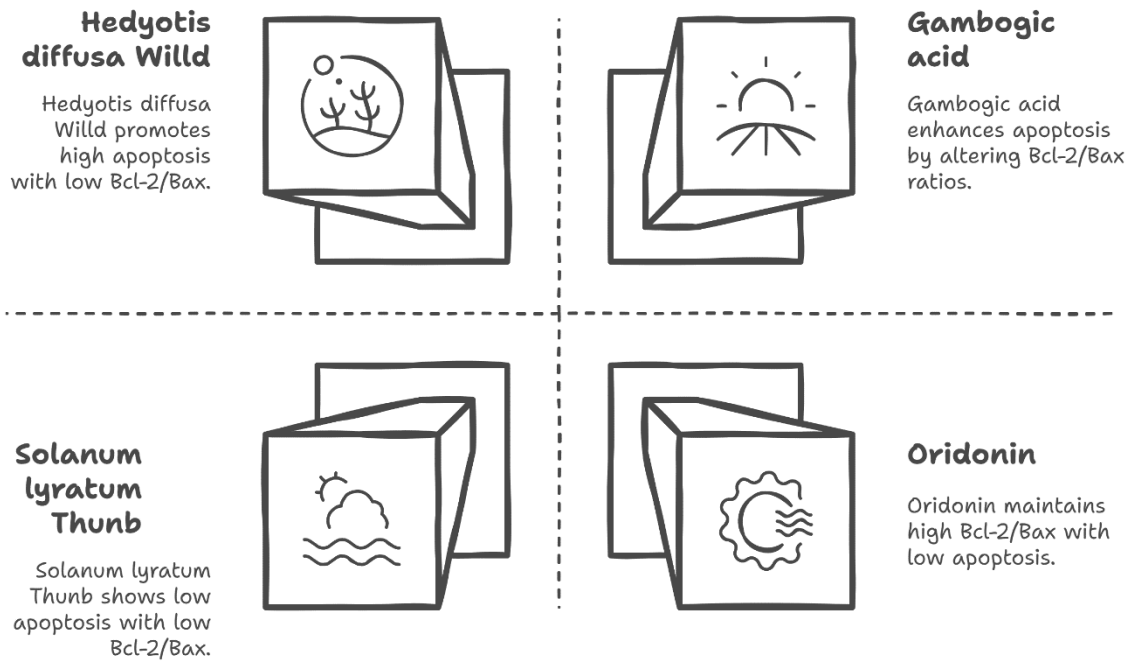

Figure 3.1: Impact of traditional Chinese medicine on apoptosis regulation

Traditional Chinese Medicines (TCMs) That Inhibit The NF-B Pathway

Five Rel-domains are found in the NF-B family of transcription factors, all of which play a role in carcinogenesis and chemoresistance [26]. The NF-B pathway is regulated by the inhibitory kinases (IKKs) of type B (IB), and it has been proven that NF-B is overexpressed in almost all of the cancer cells that have been examined up until this point. There is a correlation between chemotherapy resistance and the activation of NF-B, The anticancer effectiveness of many different cancer therapy medications can be improved by lowering this parameter [27]. Cell cycle inhibition or downregulation of the MAPK pathway were shown to be the key mechanisms by which blocking NF-kB increased pro-apoptotic activity. Traptolide, minnelide, and RA-XII as well as RA-XII, rubiarbonol G and wagonage are also included, and paeoniflorin, are anticancer TCM active chemicals that largely disrupt NF-B signaling pathways. The main diterpenoid triepoxide T. wilfordii Hook. f. (Celastraceous) was found and extracted as a TCM treatment for rheumatoid arthritis in China, where it has been used for a long time. Although TP is most commonly used to treat rheumatoid arthritis, it has recently attracted a lot of attention in cancer research and could be turned into a novel anticancer agent. The anticancer activity of TP is dependent on the five-membered unsaturated lactone D ring, with the c19 location being particularly polarity sensitive. Because of its capacity to elicit apoptosis in cancer cells of diverse types, TP has been shown to be a strong anticancer agent in trials[28]. Mechanistic studies further revealed that its anticancer impact is virtually entirely due to interfering with the NF-kB signalling system. Additional to this, in lung cancer cells, the protein TP competes with IKK for IKK binding to block NF-B activation and nuclear translocation in the presence of IKK. ERK1/2 and p38 are activated as a result. Anticancer drug resistance could be overcome and effectiveness increased by suppressing NF-B with TP and chemotherapeutic medicines [29]. A new heat shock protein 90 inhibitor, BIIB021, and TP, was demonstrated to suppress thyroid cancer cells via blocking NF-B signal pathways. The synergistic lethal impact of TP and sodium cantharidinate on human hepatoma 7721 cells was shown to be due to an increase in capase-3 activity and a decrease in NF-B activity. The anti-

angiogenic and anti-cancer effects of TP and ionising radiation treatment for nasopharyngeal carcinoma were synergistically improved by suppressing NF-B p65 phosphorylation [30]. To increase solubility and antitumor activity of Minnelide, a TP analogue, was developed. Minnelide has been shown to reduce pancreatic cancer cell proliferation and cause the cells' death in experiments conducted both in vitro and in vivo [31], lung cancer that is not small-cell non-small-cell [32], and osteosarcoma[33], It has the potential to be turned into a therapeutically useful anticancer medication, according to the researchers. For hundreds of years, Chinese medicine has employed Xiaohongshen, the root of Rubia yunnanensis (Franch), Anemia, hematemesis, menoxenia rheumatoid arthritis, contusions and TB are all treatable with this remedy [34]. TNF- was administered to HEK 293 cells, which are human embryonic kidneys, which increased the activation of NF-B; however, five newly identified compounds strongly inhibited this activation, In the plant R. yunnanensis Diels, the IC50 values are 35.07, 0.03, 1.69, 12.64, and 1.18 M, respectively. [35]. Acute kidney impairment caused by LPS was lessened as a result of R's primary active ingredient. yunnanensis, RA-XII, which exhibits antioxidant and anti-inflammatory properties [36]. In seven human cancer cells, Rubiarbonol G, another important active ingredient, activated NF-B and JNK-mediated apoptosis, causing cell cycle arrest in G0/G1 [37]. There are some plant and fruit flavonoid chemicals that reduce NF-B activity. Scutellariabaicalensis Georgi (Labiatae) is a popular TCM and used for “清热泻火, heat-clearing and fire-purging” reduce the swelling and pain associated with a sore throat, according to "Compendium of Materia Medica." Sc. baicalensis Georgi produced three active flavones: wogonin, baicalein, and baicalin, which all inhibited NF-B activity and so had anticancer potential against a variety of cancer cells [38]. Traditional Chinese Medicine (TCM) practitioners in China have long employed the root bark of Lyciumchinense Miller (Solanaceae) as an anti-inflammatory. Trans-N-caffeoyltyramine appears to be the primary molecule responsible for NF-B suppression in studies using six pure chemicals identified and extracted from the cortex lyciiradicis. More research into the structure–activity relationship has revealed that trans N-caffeoyl tyramine's inhibitory impact on NF-B is linked to structural components of the Michael acceptor type [39]. As reported in a second investigation, the in vitro and in-vivo effects of a crude cortex lyciiradicis extract on proliferation and migration were both profound, with elevated pro-apoptotic proteins caspase-3 and Bax and decreased antiapoptotic components Bcl-2 [40]. Rheumatoid arthritis in China has been treated for over a thousand years with Paeonia lactiflora Pall (Ranunculaceae), a plant native to China. P. lactiflora Pall root's principal bioactive constituent, paeoniflorin, suppressed the NF-B transcriptional activity in human colon cancer HT-29 cells activated by LPS, according to a study [41]. The cytotoxicity of Nigella sativa (Ranunculaceae family) oil was mediated via the regulation of the NF-B signalling pathway. Carcinogens were slowed down by the anti-cancer properties of the oil of Nigella sativa (Ranunculaceae family). Human lymphoma U937 cells can be cytotoxic and promote the apoptosis of N. sativa extract, but not normal human vascular endothelial ECV304 cells [42].

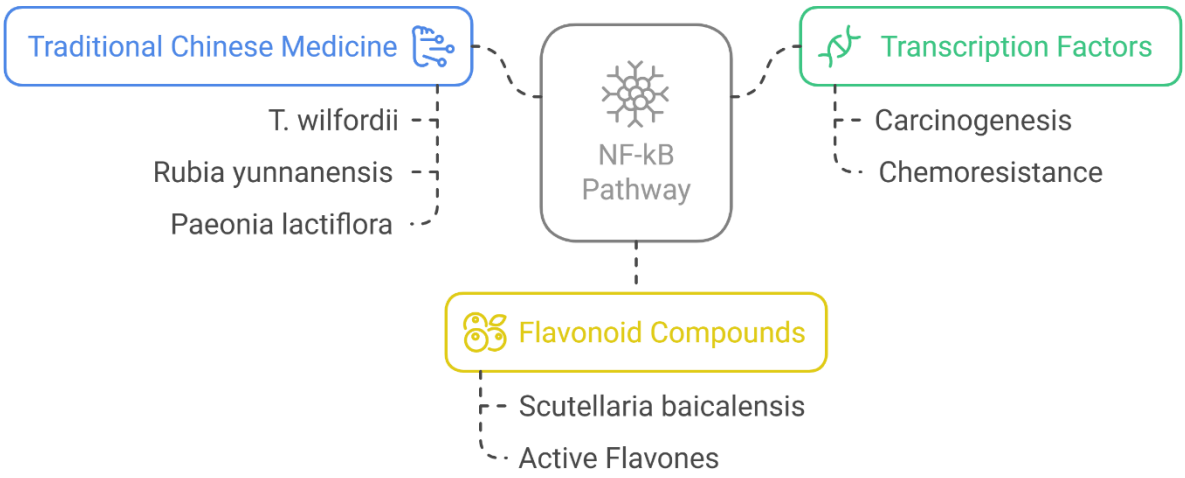

Figure 3.2: NF-Kb pathway in cancer treatment

Anticancer TCMs Through Activating Reactive Oxygen Species

The production of reactive oxygen species (ROS) by oxygen-derived molecules such superoxide, hydrogen peroxide, singlet oxygen, and the hydroxyl radical is essential for the process of apoptosis as well as the progression of cancer. Reactive oxygen species (ROS) are produced by anticancer medicines (ROS), which mostly accumulate in cancer cells' mitochondria, where they activate apoptotic signalling pathways such PI3K/Akt, MAPKs, and NF-B, as well as the tumour suppressor p53, causing cancer cell damage and death [47]. As a result, it's a good idea to look for and develop anticancer drugs that cause cancer cells to produce excessive amounts of ROS. Many anticancer TCMs have been shown to boost ROS levels and promote apoptotic cell death in cancer cells, including Pleurotus polysaccharides, jaridonin, and longikaurin A. ROS is known to be a potent anticancer agent, thus this is intriguing. Curcumin, a natural component of food that has been utilised for millennia, is extracted from the root of the plant Zingiberaceae, which is known scientifically as Curcuma longa Linn. The natural compound known as curcumin has been extracted, purified, and standardised. The curcumin found in TCM has multiple beneficial benefits, including those of an anti-inflammatory, an anti-angiogenesis, an anti-oxidant, and a cancer preventative. Curcumin has been demonstrated to promote reactive oxygen species (ROS) generation, which in turn causes human osteosarcoma MG63, COLO-16, and A549 cells to undergo apoptosis. [43]. Curcumin has been shown in earlier research to increase ROS generation, which causes cytotoxicity and death in lung cancer A549 cells. Curcumin may also enhance cisplatin's anticancer effects in bladder cancer cells 253J-Bv and T24 through a ROS-mediated mechanism[44]. Due to its modest absorption and pharmacokinetic features, curcumin's therapeutic value in cancer therapy is limited. This has resulted in the development of new anticancer medicines with increased bioavailability and stability in curcumin derivatives such as B63, EF24, WZ26, WZ35, L48H37, and MAC CA10 [45]. In both in vitro and animal experiments on colon cancer SW620 cells, the anti-cancer effect of this monocarbonyl analogue of curcumin was found to be mediated by cancer cells' excessive generation of reactive oxygen species. These findings were obtained from studies on curcumin. In order to determine whether or not B19, a derivative of curcumin, had any effect on human gastric cancer cells, it was used in vitro to inhibit the growth of SGC-7901, BGC-823, and KATO III, and in vivo to generate reactive oxygen species (ROS)

and stress the endoplasmic reticulum (ER) in order to inhibit the growth of human gastric cancer xenografts that were made with SGC-7901 [46]. A novel curcumin EF24 derivative significantly inhibited cell proliferation and induced death in colorectal cancer cells HCT-116, HT-29, and SW-620. This was accomplished primarily by the production and accumulation of reactive oxygen species (ROS). An analogue of curcumin known as WZ26 demonstrated anticancer efficacy that was superior to that of curcumin when tested on human gastric cancer tumour xenografts in vivo. In vitro, WZ26 inhibited ROS overproduction and cell proliferation in gastric cancer cells at a similar level of potency as curcumin. Cytotoxicity in vitro and apoptosis induction in vivo greatly decreased CT26 xenografts as a consequence of WZ35's ROS-mediated signalling against colon cancer CT26 cells. WZ35 inhibited cell proliferation and increased cell apoptosis in prostate cancer RM-1 and DU145 cells, as well as lowered the rate of tumour growth in RM-1 homograft tumour tissues in vivo. This was accomplished via inducing apoptosis and increasing the formation of reactive oxygen species (ROS). WZ35 was able to suppress the proliferation of HCCLM3, HepG2, and Huh-7 cells, as well as migration and invasion, and it was also able to decrease the HCCLM3 tumor's ability to metastasize in vivo [49]. It has also been reported that L48H37, a novel non-toxic analogue of curcumin, can inhibit the proliferation and colonisation of human lung cancer cells. It does this by increasing ROS production and reducing tumour growth in xenogenets that have lung cancer. MAC CA10 is a novel allylated monocarbonyl analogue of curcumin. This activation of the ROS-mediated signalling mechanism has been confirmed in vitro, and its anticancer activity has been demonstrated in vivo in a tumour xenotic animal model [47]. K-carrageenan, for instance, is an efficient transporter that can enhance the anticancer action of other substances. An excessive amount of reactive oxygen species (ROS) formation led to the death of lung cancer cells by apoptosis. In the investigations that looked into the effects of k-carrageenan loaded with curcumin, A549 cells were employed as the subjects [48]. It was shown that curcumin that had been treated with folic acid was more biocompatible than free curcumin in breast cancer MCF-7 cells, and that it was more effective in inhibiting cell growth by raising intracellular ROS formation. This was the case in both of these regards. Burns, sore throats, macular eruptions, carbuncles, and measles are some of the conditions that have traditionally been treated using the dried root of Lithospermum erythrorhizon in traditional Chinese medicine [49]. It has been established that human cancer cells can be destroyed by the napthoquinone Shikonin, which is derived from the roots of the plant L. erythrorhizon and stimulates the generation of ROS. Shikonin can also prevent the creation of A549 tumour xenografts by preventing the growth of human lung cancer A549 cells, causing these cells to die, and increasing the quantities of reactive oxygen species (ROS) produced within the cells. Shikonin inhibited the growth of HL-60 human leukaemia cells by targeting the cytosolic form of thioredoxin reductase. This resulted in an increase in the level of ROS-mediated cell death. [50]. SNU-407 colon cancer, Hep-G2 liver cancer, MDA-MB-231 breast cancer, and Ishikawa, HEC-1A, KLE, and RL95-2 endometrioid endometrial tumour cells have all shown Shikonin to decrease cell growth and increase cell death [51]. shikonin overproduction of ROS and ROS scavengers were found to impair the anticancer activity of the substance in further studies on Huh-7 and BEL7402 liver cancer cells in vitro and in vivo. Shikonin was employed to boost ROS production, which improved apoptosis in gefitinib-resistant H1650 and H1975 lung cancer cells. Shikonin appears to be useful in treating human breast cancer metastasis because it prevents MDA-MB231 cells from migrating and invading.[52] Shikonin oxime derivatives, which have 45 sulfur-containing Shikonins, were found to stop cancer cell growth and cause apoptosis in breast cancer MCF-7, gastric tumour MGC-803, liver tumour Bel7402, and colon cancer HCT-15 cells, but not in normal human skin fibroblast HSF cells. Pl. abalonus (Agaricaceae) is an edible polysaccharide supplement. Polysaccharides from Pl. abalonus were found to exhibit anticancer and antioxidant effects in experiments. When crude

polysaccharides from Pl. abalonus were introduced to PAP-3 and MCF-7 breast cancer cells, they stopped proliferating and destroyed the cells by producing too many ROS [53]. Insects that are classified as belonging to the genus (Hemsl). Antibacterial, antioxidant, anti-inflammatory, and anticancer properties have been found in H. Hara (Lamiaceae), a supplement that is popular in China. Jaridonin is a novel diterpenoid that was discovered in I. rubescens and isolated from the plant (Hemsl). Apoptosis caused by reactive oxygen species was induced in three different human esophageal cancer cell lines. apoptosis as well as a reduction in cell development [54]. A diterpenoid from Rabdosiaternifolia (D. Don) H. Hara (Labiatae) known as longikaurin A has been used in Traditional Chinese Medicine. By causing apoptosis, G2/M cell cycle arrest, and ROS overproduction, Longikaurin A slowed the growth of SMMC-7721 liver cancer xenografts both in vitro and in vivo. Longikaurin A induced apoptosis and inhibited oesophageal cancer KYSE-30 cells and xenogeneic tumours in vitro and in vivo, respectively. In vitro studies have shown that Longikaurin A, for example, can reduce cell proliferation, induce apoptosis, and suppress the growth of CNE2 tumour xenografts [55]. Physalisalkekengi franchetii L. Physalisalkekengi franchetii L. (Mast). Makino (Jindenglong) has been used to cure sore throats, coughs. The Chinese have been troubled by a variety of ailments for thousands of years, including excessive phlegm, pemphigus, pharyngitis, eczema and jaundice. Bioactive withanolide Physalin A was found in the Ph. Lvar franchetii plant and is a bioactive withanolide (Mast). Makino may be able to increase ROS production in human melanoma A375-S2 cells, resulting in cell death and inhibition of cell growth. In human lung cancer A549 cells, physalin A boosted ROS generation, limiting cell growth and encouraging apoptosis and G2/M arrest. Ph. L. was also used to purify physalin B. var. franchetii franchetii franchetii (Mast). Makino decreased colon cancer cell proliferation and expedited apoptosis in individuals by increasing mitochondrial ROS production. HCT-116 cells in the body can cause cancer. [56]. A recent study found that MCF-7 breast cancer cells and A549 lung cancer cells are not able to multiply. [57].

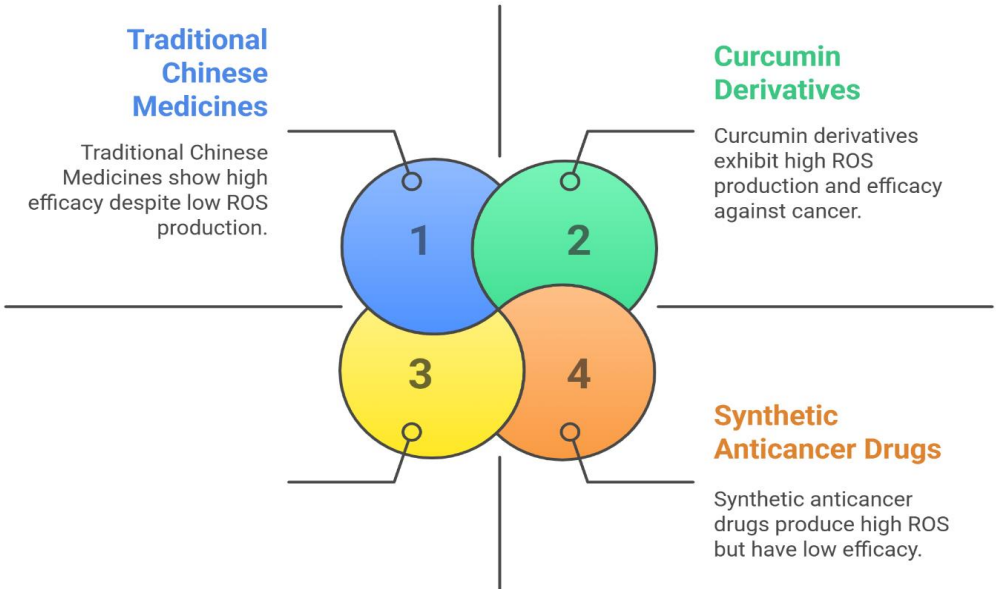

Figure 3.3: Categorization of anticancer agents by ROS production

Anticancer TCMs Through Targeting Pi3k/Akt/Mtor Pathway

The PI3K/Akt/mTOR pathway is activated by tyrosine kinase growth factor receptors, which are important for cell growth and survival. Tensin homolog negative regulator is a protein that blocks

this pathway. It resembles other apoptotic pathways in many ways (PTEN). The PI3K/Akt/mTOR pathway has been linked to cancer growth as well as therapy resistance. Anti-Akt-mediated cell death has also been linked to autophagy. Silybin (Silibinin), Matrine, MASM, WM130, and YYJ18 are anticancer compounds derived from TCMs that largely inhibit the PI3K/Akt/mTOR pathway. In China, Silybum marianum (milk thistle) has been used to treat Amanita phalloides toxicity, cancer, and liver disease. In the seeds of Si. marianum, an active flavonolignan known as silybin has been identified. The PI3K/Akt-mTOR signalling pathway is blocked in Hep3B liver cancer cells and HeLa cervical cancer cells by silybin, a drug that has been shown to inhibit cell growth and death [58]. Apoptosis was triggered in MCF-7 and SKBR3 breast cancer cells, in A549 lung cancer cells, in HT-29 colon cancer cells, in Panc-1 and AsPC-1 pancreatic cancer cells, as well as in BxPC-3 pancreatic cancer cells when silybin was administered. In the liver cancer cells SNU761 and Huh-BAT, the ovarian cancer cells SKOV-3, and the LN229 glioma cells, silybin may improve the anticancer activity of sorafenib, gefitinib, paclitaxel, and temozolomide. When silybin was added to regorafenib, the PI3K/AKT/mTOR pathway was reduced more than when regorafenib and silybin were used separately. This improved treatment efficacy and extended overall median survival [59]. Chinese Traditional Chinese Medicine uses the herb Sophora flavescens (SF) to treat cancer and inflammation. An SF alkaloid was used to isolate and purify matrine. In human breast, prostate, and bladder cancer cells, matrine inhibited the PI3K/AKT pathway, leading in lower cell proliferation, mortality, and multidrug resistance reversal. The carbon–carbon double bond at position 14′ of matrine's skeleton, according to the structural research, is crucial to the compound's anticancer action. In vitro studies have shown that a number of MASM compounds can successfully suppress cell proliferation and trigger apoptosis in human liver cancer Hep3B and Huh-7 cells, as well as significantly limit Huh-7 xenograft growth. It was also discovered that the matrine derivative WM130 (C30N4H40SO5F) inhibited liver cancer cell proliferation, migration, and invasion while inducing apoptosis. In both the lab and the animal model, PTEN/Akt inhibitors reduced tumour growth in Huh-7 xenografts. The new matrine derivative YYJ18 (14-Thienyl methylene matrine) inhibited and cancerous cells in the CNE1, CNE2, and HONE1 cell lines through the PI3K/Akt and MAPK pathways triggered apoptosis [60].

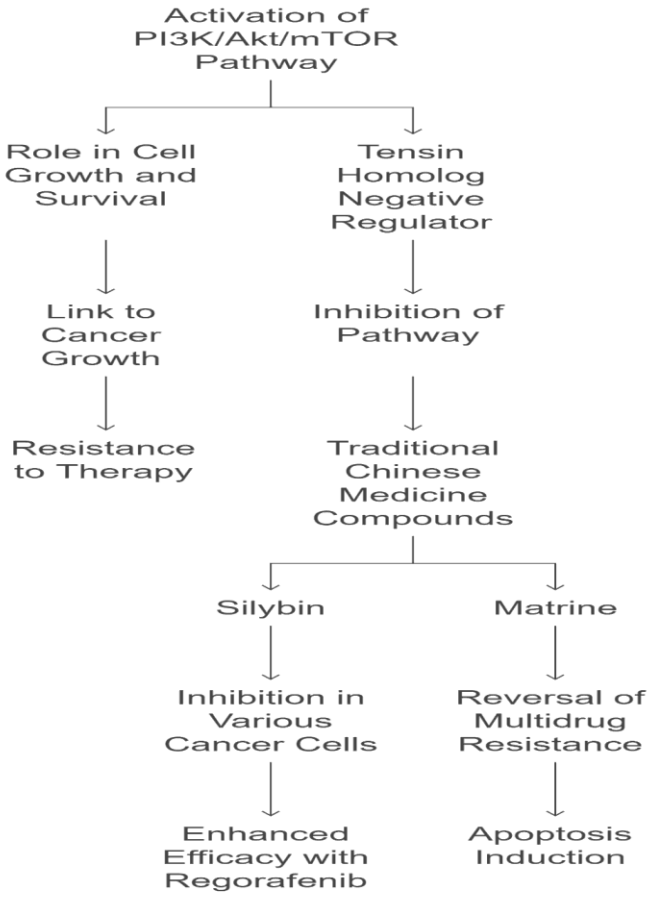

Figure 3.4: Inhibition of P13K/AKT/MTOR

Anticancer TCMs Through Targeting Jak-Stat3 Signal Pathway

Because they are active and overexpressed, Janus kinase (Jak) signal transducer and STAT3 are critical for cancer cell survival and death. An unfavourable prognosis in patients with colorectal cancer was linked to elevated levels of p-STAT3, a STAT3 activation variant. Several research have shown this to be true. The survival and death of cancer cells depend on the overexpression and activation of the Janus kinase (Jak) signal transducer and the STAT3 transcription factor. The Jak-STAT3 signalling pathway, which is a potential target for anticancer therapy, can be blocked to aid in the development of new treatments. By inhibiting the Jak-STAT3 signalling system, anticancer TCM active compounds such as cucurbitacin B and 5,7-dihydroxyflavone cause apoptosis and decrease cancer cell proliferation. Cucurbitacin B, a triterpenoid tetracyclic triterpenoid tetracyclic triterpenoid tetracyclic triterpenoid tetracyclic triterpenoid tetracyclic triterpenoid tetracyclic triterpenoid tetracyclic triterpenoid tetracyclic triterpenoid Cucurbitacin B, alone or in conjunction with other chemotherapeutic drugs targeting the JAK/STAT3 pathway, was found to decrease cancer cells such as MKN-45 gastric cancer, Panc-1 pancreatic cancer, MiaPpaCa-2, PL45 neuroblastoma, and osteosarcoma U2 OS [61]. By altering the structure of cucurbitacin B, DACE, a semisynthetic derivative, was discovered to have powerful anti-cancer actions on lung cancer cells. Targeting the STAT3, AkT, and ERK signalling pathways enhanced solubility and bioavailability in vivo and significantly slowed the growth of c-RAF-induced lung cancers in vitro [62]. For more than 2,000 years, Artemisia annua L. has been used in China to treat fever. Artemisinin, a natural chemical discovered and extracted in China in the 1970s, is an

effective treatment for malaria resistance. In 2015, Professor Youyou Tu received the Nobel Prize in Physiology or Medicine for her role in the discovery of artemisinin [63]. Antischistosomiasis, antiviral, and anticancer properties are just a few of the biological and pharmacological effects of artemisinin. Artemisinin has been found to kill cancer cells selectively while inflicting minimum harm to normal cells. On the basis of research on human head and neck cancer cells, scientists have found that DHA, an artemisinin derivative that is more water-soluble, significantly inhibits cell growth while simultaneously increasing apoptosis. Hep-G2 liver cancer cells, HCT-116 colon cancer cells, and Cal-27 tongue cancer cells were studied in this study [64]. In human umbilical vein endothelial cells, 20 M DHA induced temporary activation of JNK. BDL301 is a traditional Chinese medicine that has been used to treat inflammatory illnesses for hundreds of years. By interfering with the STAT3 signalling system, BDL301 suppressed cell proliferation, reduced CT-26 tumour development, and triggered apoptosis in colorectal cancer (CT-26, HCT-116) cells. [65]. Eriobotrya is Eriobotrya in Japanese (Thunb). In China, cancer supplements such as Lindl (Rosaceae) and Ziziphus jujuba Miller (Rhamnaceae) from traditional Chinese medicine are used. Urasolic acid (UA), a small pentacyclin triterpene chemical, was generated by E. Agave. The UA had been carefully cleaned (Thunb). Z. Using the JNK, PI3K/Akt, and NF-B pathways, Lindl Jujuba Miller and colleagues reduced the growth and death of human pancreatic cancer Panc-1, MIA PaCa-2, and Capan-1 cells. In human liver cancer SK-Hep-1 cells, the JNK/MAPK, PI3K/Akt, and p38 signalling pathways were discovered to be responsible for UA's anticancer effects. Another study discovered that through stimulating the pro-apoptotic ASK1/JNK signalling pathway, the UA decreased the proliferation of bladder cancer T24 cells and caused them to die. [66]. There was no damage to the normal hepatocyte L-O2 cells when dietary flavonoid 5,7-dihydroxyflavone was used in vitro against human liver cancer HepG2 cells and considerable suppression of the formation of HepG2 tumour xenografts in vivo by reducing STAT3 phosphorylation [66].

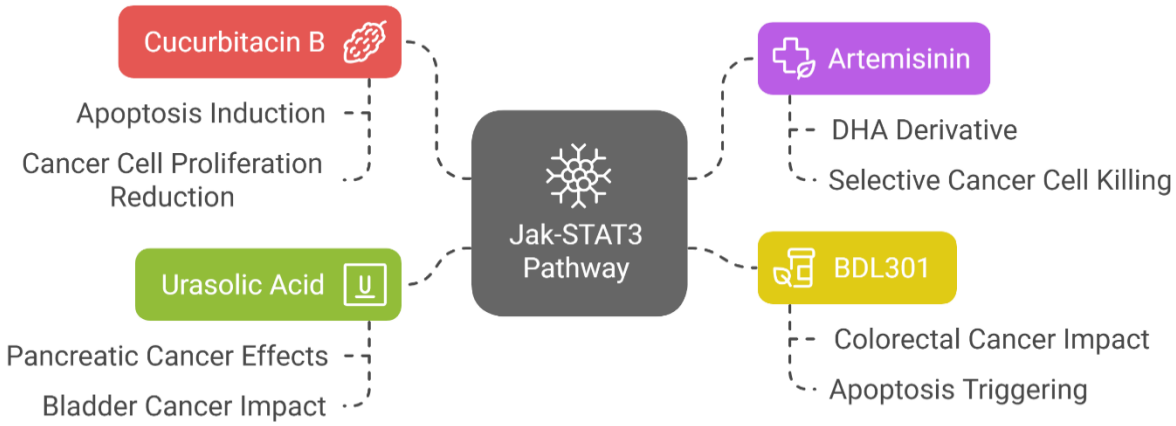

Figure 3.5: Targeting Jak-STAT3 Pathway in cancer treatment

Anticancer TCMs Through Targeting Multiple Apoptotic Pathways

Traditional Chinese Medicines (TCMs) are effective against cancer because they act as multitarget molecules, attacking multiple cellular signalling pathways at once. This is in contrast to conventional pharmaceutical medicines, which only aim to treat a specific disease. Anticancer traditional Chinese medicines (TCMs) and the therapeutic chemicals generated from them have an

important quality in common: the ability to target a diverse collection of cellular signalling pathways. Seed extract from Coixlacryma-jobi L. This plant contains a number of different chemicals, some of which are known as (Yadanzi), evodiamine (EVO), compound K, rh2 and rk3 ginsenosides, and Bruceajavanica oil emulsion injection. Icariside II, osthole (OST), rh2 and rk3, as well as compound K are some examples of further chemicals. When it comes to treating tiredness, Chinese herbal treatments like Herbaepimedii have been in use for decades. Cancer cells are inhibited in proliferation and death by the flavonoid glycoside, Icariside II, from H. epimedii, which interacts with a number of signalling pathways. Icariside II has been demonstrated to increase the expression of Bax, cleaved caspases-3,-7, and 9, as well as poly (ADP-ribose) polymerase, which inhibits cell growth and causes cell death in U2OS cells [67]. When compared to Icariside II-treated cells, A549 and H1299 human lung cancer cells displayed reduced EMT, migration, and invasion after being exposed to an inflammatory environment induced by TNF-. [68]. It belongs to the genus Cnidiummonnieri and species Cnidiummonnieri (L). In China, Vietnam, and Japan, cusson is one of the traditional Chinese medicines (TCMs) that is used the most frequently to treat a wide variety of medical conditions, including male impotence, female genital disease, hypothermia, and other skin-related issues. Anti-pruritic, anti-pruritic, anti-dermatophytic, and anti-allergic are only few of the many beneficial effects that this substance possesses. The dried fruit of Cn. monnieri was utilised in the process of locating and extracting OSTs (L). Targeting several apoptotic signalling pathways, as discovered by Cusson and colleagues, In vitro and in vivo, tumour development was dramatically reduced in a variety of animal models of tumour xenografts. OST suppresses osteosarcoma cell growth by boosting the Bax/Bcl-2 ratio and lowering caspase-3 synthesis, according to preliminary studies in osteosarcoma MG-63 cells [69]. This method destroyed osteosarcoma MG-63 and SAOS-2 cells in the lab, restricting cell development. After OST medication, the PI3K/Akt pathway was reduced in HCCC-9810 and RBE cells from the intrahepatic liver. The apoptotic proteins Bcl-2, Bax, and Caspase 3/9 were changed in ovarian cancer A2780 and OV2008 cells treated with OST. The ability of TRAIL to elicit cell death in human cancer cells MDA-MB-231, Caki, and U251MG was improved when C-FLIP was downregulated. The minimal water absorption of OST further limits its therapeutic efficacy in humans. When OST/CA-TMC micelles were applied to human breast and cervical cancer cell lines, they demonstrated substantial anticancer activity [70]. Since ancient times, practitioners of traditional Chinese medicine (TCM) have used Evodia rutaecarpa to cure a variety of painful conditions, including nausea, vomiting, and diarrhoea. The quinolone alkaloid known as EVO, which was found in E. rutaecarpa, was successfully isolated. EVO is a one-of-a-kind quinolone alkaloid that is taken from the plant where it was originally discovered. [71]. HO-8910PM Cell proliferation and apoptosis EVO's capacity to cause G2/M cell cycle arrest in human ovarian cancer cells may reduce growth and death. EVO Apoptosis and cell proliferation were reduced in osteosarcoma MG-63 and SAOS-2 cells in response to the PTEN/Akt pathway. In HCCC-9810 and RBE cells originating from intrahepatic cholangiocarcinoma, OST suppressed the PI3K/Akt signalling pathway. The ability of OST to target the PI3K/Akt and MAPK signal pathways lowers OV2008 ovarian cancer cells in C6 rat glioma and A2780 ovarian cancer cells. In human cancer cells MDA-MB-231, Caki, and U251MG, the FLICE-like inhibitory protein was downregulated, boosting TRAIL's potential to cause cell death (c-FLIP). The ability of OST to absorb water in humans is likewise limited, which limits its applicability. In human breast cancer MCF-7 and cervical carcinoma Hela cells, TMC micelles were investigated for their capacity to cause cell necrosis" (apoptosis). Cell growth was inhibited in A2780, A2780CP, ES-2, and SKOV-3 cells when JNK and PERK were activated. Human lung cancer H446 and H16 cells, as well as human colon COLO205 and HT-29 cells, have mitochondrial and ER pathways, were found to decrease cell growth and enhance apoptosis by another study [72]. In human lung cancer cell lines A549 and

H1299. after 24–48 hours of treatment with EVO at 20–40 M, the Bax/Bcl-2 ratio increased and cell proliferation reduced. These effects were also seen in the A549 and H1299 human lung cancer cell lines. Growth suppression, apoptosis induction, and cell-cycle arrest were all observed in SGC-7901 cells after treatment with EVO. The Bax/Bcl-2 ratio varies when Caspase-3,-8, and 9 are engaged. EVO's anticancer properties have been linked to the Her2/AkT/Bcl-2 signalling pathways. EVO increased the levels of p21 and p53 in TPC-1 and SW1736 thyroid cancer cells, but decreased the levels of Bcl-2, phospho-Akt, and matrix metalloproteinases-2 and-9. As apoptosis increased, cell proliferation, migration, and EMT all reduced. We developed a way to stop a human kidney cancer cell line from growing. A498, apoptosis was induced, and cells were arrested as a result of EVO treatment. In vivo, proteolytic phosphorylation of Bcl-2, stress proteins, and RNA-binding proteins may also inhibit the growth of A498 tumours. By boosting the concentration of specific proteins in the body, EVO may cause these adverse effects [73]. According to the "Compendium of Materia Medica," Panax Ginseng C. A. Mey (Araliaceae) has "buzhongyiqui" properties (reinforcing the centre and enhancing energy). According to pharmacological study, P. Ginseng C. A. Mey formulations offer anticancer, antidiabetic, antiaging, antifatigue, and antistress properties, as well as pain relief and enhanced cognitive and sexual performance, immune and liver function enhancement, and so on. P. ginseng C. A. Mey formulations have been found to have anticancer potential in multiple preclinical and clinical investigations, and the anticancer activity is primarily due to ginsenosides [74]. Cancer of the colon in humans HCT-116 cells stopped in the G0/G1 phase of the cell cycle due to increased cleaved caspase-3 and Bax production in the ginsenoside, water extract, and polysaccharide fractions. Ginsenoside Rh2 (purified ginseng saponin) may suppress human lung cancer A549 cell proliferation by activating caspases-2,-3, and-8 and boosting the expression of TRAIL-RI (DR4) death receptors. HeLa cells are found in human cervical carcinomas, Rh2 was found to activate Fas ligand independently, leading to an increase in apoptosis. These two ginsenoside-derived compounds were found to interact with the p38/MAPK signalling pathway, Apoptosis was induced in CRT-MG cells from patients as a result. Rk3 inhibited the development and mortality of H460 and A549 lung cancer cells in vitro, while the cell cycle was also disrupted. Additionally, Rk3 significantly delayed the formation of tumours in H460 xenografts without causing any clear host damage [79]. In human leukaemia U937 cells, an extract of red ginseng sped up the process of apoptosis and reduced cell proliferation. This was accomplished by activating caspase-3, Anti-apoptotic proteins Bcl-2 and X are reduced (L), and inhibiting the action of telomerase. As the principal active ingredients in the herb's root, ginsenosides and compounds synthesised from them have been found in laboratory and animal experiments to possess anticancer properties, the term "ginkgosides" is used interchangeably. Because of the control of protein-kinase activity, growth factors and cell proliferation, as well as death mediators, these anticancer effects are achieved (p53 and p21). The bacterium known as B. javanica can be found in Java (L). According to the 16th-century "Compendium of Materia Medica," Corns and warts were treated with Merr. (Simaroubaceae). An increase in caspases 3 and 9 and a decrease in COX-2 and NF-kB were found to be responsible for B, javanica oil to limit the development of bladder cancer T24 cells while simultaneously promoting cell death [75]. B. Javanica seed oil inhibited tumor xenograft growth, as well as apoptosis and cytotoxicity, when administered to human AML U937 cells in a lab setting. The apoptotic signalling pathway was influenced by B. javanica fruit extract, which decreased cell growth and caused apoptosis in PANC-1, SW1990, and CAPAN-1 pancreatic cancer cells. According to studies, B. javanica oil emulsion induces apoptosis while inhibiting autophagy in colon cancer HCT-116 cells [81]. Apoptosis and G0/G1 cell cycle arrest occurred when p53 and Bcl-2 levels were reduced in SMMC-7721 liver cancer cells (Ma and Zhang, 2004). B. javanica oil emulsion reduced cell proliferation by triggering apoptosis and decreasing hypoxia-inducible

factor 1 (HIF-1) and increased radio sensitivity in ECA109 cells and ECA109 tumors in vivo (HIF-1). Phase II clinical studies were conducted on advanced lung cancer patients, and it was determined that pemetrexed and platinum, when combined with the oil emulsion injection from the B. javanica plant (Yadanzi®), produced higher levels of anticancer activity while having less severe side effects. An overall response rate of 85.3% in 75 patients with advanced gastric cancer was achieved by combining Yadanzi® injection with chemotherapy in a different phase II clinical investigation [76]. In 2,234 patients with advanced non-small cell lung cancer, B. javanica oil emulsion increased effectiveness and reduced chemotherapy-induced side effects such as nausea and leukopenia (NSCLC). Yadanzi®, a seed oil emulsion prepared from B. javanica (L. Merr.) seed, has been licenced by China's Food and Drug Administration as an adjuvant therapy for patients with lung and prostate malignancies (CFDA). It has been estimated that C. lacryma-jobi L. has been utilised to treat various ailments in Chinese medicine for the better part of a millennium. In research, C. lacryma-jobi L. was found to exhibit anticancer, antimutagenicity, anti-proliferation, antioxidant, anti-inflammatory, anti-ulcer, antibacterial, and antiallergenic properties. A methanolic extract of C. lacryma-jobi L. seed inhibited cell growth, apoptosis, and cell cycle arrest. A549 cells cultured in the laboratory, and decreased COX-2 expression in A549 xenografts in vivo, considerably reducing tumour growth [77]. Bioactive subfraction of C. lacryma-jobi L. bran ethanolic extract decreased the development of MCF-7, MDA-MB-231, and T-47D human breast cancer cells. Five newly discovered and isolated chemicals from C. have been demonstrated to be highly hazardous to human lung and colorectal cancer cells. lacryma-jobi L., and the inhibitory concentration (IC50) ranged from 28.6 to 72.6 mg/ml. Cell proliferation and doxorubicin sensitivity may be significantly reduced by C. lacryma-jobi L. ethanolic extracts' hexane fraction, which triggers apoptosis and lower P-gp expression in human uterine sarcoma parent and doxorubicin resistant MES-SA/Dx5 cells, respectively. When the seed of C. lacryma-jobi L. was discovered in 1995, scientists derived kanglaite (KLT) injectable from it, which was licenced by the CFDA in 1995 and Roszdravnadzor in Russia in 2003 as an anticancer drug. Various cancer cells in vitro and tumours in vivo responded favourably to KLT injections, according to research [78]. KLT increased the expression of p53, P21WAFI/CIPI/PCNA, and caspase-3 in cancer cells while lowering the expression of cyclins A, E1, and F, which resulted in the death of these cells. This was achieved by boosting the expression of the first three genes. KLT was found to have immunomodulatory properties in another study. Mice with human liver cancer in its nude form In patients with liver cancer, xenografts of the HepG2 strain reduced serum levels of interferon (IFN) and interleukin (IL)-2, boosted the cytotoxic activities of natural killer (NK) and CD8+ T cells, and promoted the immune response by raising T and NK cell numbers in the blood. The results of this study were published in the journal Experimental Hepatology. Oncogenes LoVo and CT26 were treated with KLT in a clinical trial, in addition to CT26 tumours, which resulted in decreased NF-B expression and increased connexin 43 expression. According to clinical trials and meta-analyses, combining KLT with chemotherapeutic medications improved response rates, symptoms, and quality of life in patients with primary NSCLC while lowering the negative effects caused by chemotherapy [79], unresectable hepatocellular carcinoma [80], gastric cancer [81], or pancreatic cancer[82]. The process of drying the skin of toads results in the production of venenumbufonis, which is a well-known component of traditional Chinese medicine. Two of the numerous beneficial things that it may do for you are reduce swelling and eliminate toxins, and those are just two of the many uses it has. In traditional Chinese medicine, venenumbufonis was utilised as a cardiotonic, diuretic, painkiller, and treatment for cancer and inflammatory illness. Additionally, it was used as a treatment for inflammatory disease. In the 1990s, China developed an injectable preparation of V. bufonis for the purpose of treating cancer under the name huachansu. This preparation was given the name huachansu. According to the findings of the study

that was carried out, the apoptotic effect that coxibufacin had on liver cancer cells was caused by the caspase-mediated apoptotic pathway. In a study in which 76 people with stomach cancer participated, the anticancer activity of cinobufacin was shown to have significantly risen, while the drug-induced toxicity was found to have significantly decreased. As a direct result of this element, the patients experienced an improvement in their quality of life in general. cinobufacin was coupled with either cisplatin, docetaxel, or 5-fluorouracil in the course of this particular research endeavour[83].Bufotalin, a cytotoxic compound derived from the V. bufonis plant, was found to inhibit cell growth more effectively in doxorubicin-induced multidrug resistant, When compared to the parent HepG2 cells, R-HepG2 cells; R-HepG2 xenograft cells grown in the absence of bufotalin were shown to form tumours at a lower rate than parent HepG2 cells. In order to induce cell death, researchers believe that bufotalin must activate caspases 9 and 3, as well as PARP cleavage and the Bax/Bcl-2 ratio, among other things, changes in intracellular calcium levels and ROS generation, and an increase in expression and inhibition of Akt phosphorylation [84]. It has been determined that the epidermis of this species includes the cardiotonic steroids bufalin and cinobufagin, and both of these compounds have been extracted and characterised. In addition to Bcl-2/Bax, p53, p21WAF1, cyclin D1, Cyt-c, and caspase 3-8 and 10, bufalin targeted signalling pathways such as Bcl-2, Cyt-c, and caspase ten as well as PARP, PI3K/Akt, JNK and the Erk family of MAP kinases [85]. Anti-tumor activity of bufalin and sorafenib may be boosted by GANT61 and cyclopamine, which block the PI3K/AkT pathway, downregulate MMP-2, MMP-9, -catenin, and upregulate E-cadherin in human liver cancer cells [86]. Apoptosis modulators such as Bax and Cyt-c, as well as caspases 3-8 and 9, are targeted by Cinobufagin in prostate cancer cells (LNCaP, DU145, and PC3) [93] and liver cancer HepG2 cells (HepG2) [87].

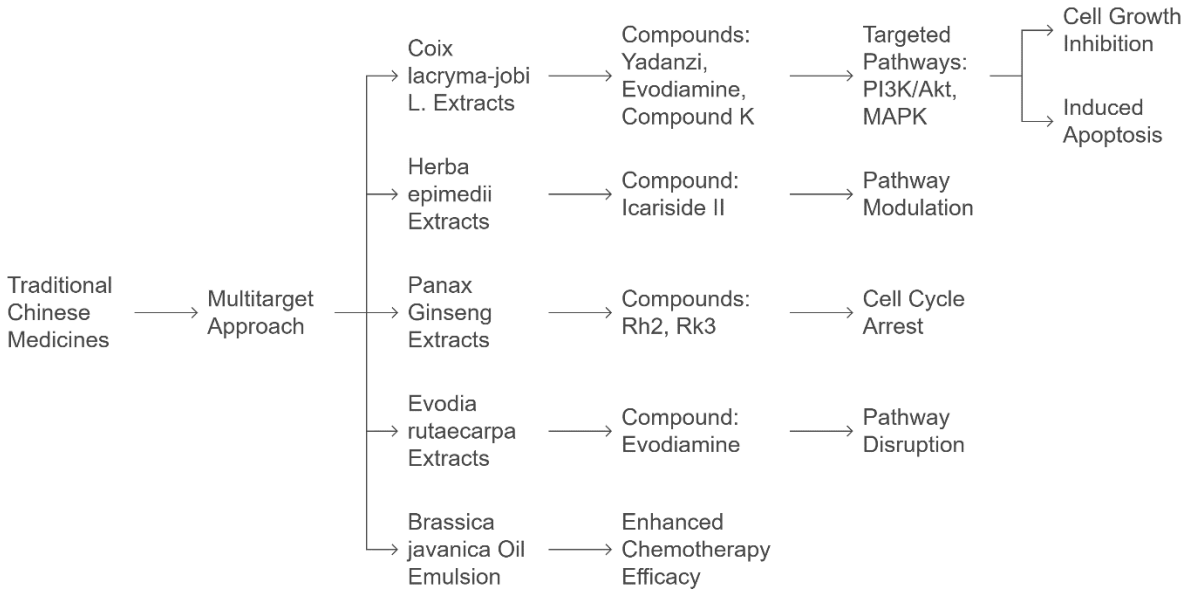

Figure 3.6: Traditional medicines and their anticancer mechani

Conclusion:

Apoptosis is a mechanism that is extremely selective, and it can take place in both unhealthy and healthy situations. During the process of cell death, which happens in all different kinds of cells and species, both the cytoplasm and the nucleus go through many transformations. It is necessary for a variety of biochemical processes to take place before one can speak of apoptosis. These

processes include the activation of caspases, the destruction of DNA and proteins, the change of membranes, and the recognition of phagocytic cells. Conventional chemotherapy is frequently utilised in conjunction with these precision-based treatments. This is something that takes place on a fairly consistent basis. On the other hand, the adverse effects of individualised chemotherapy treatments are often of a lower severity compared to those of chemotherapy medications available over the counter in generic form. In this way, cancer-targeting medications are given to patients suffering from breast cancer so that the disease might be treated. Through the use of targeted therapy, it is possible to control the growth of breast cancer cells and slow their multiplication. This is accomplished by inhibiting the activity of abnormal proteins. In order to combat breast cancer, this procedure could be performed (such as HER2). Breast cancer targeted therapies interfere with the action of certain chemicals that are required for the proliferation and survival of tumour cells in order to stop the disease from spreading. This is how breast cancer spreads. It is possible for cancer cells to overexpress certain receptors, which, when triggered, can result in the formation of cancer and promote the activation of genes that are essential for the proliferation, growth, and survival of cancer cells.

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