ORIGINAL RESEARCH PAPER

Volume-8 | Issue-7 | July - 2019 | PRINT ISSN No. 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

PHYTOCHEMICALS AND CHEMOTHERAPY: NOVEL CHEMOPREVENTATIVE TREATMENT APPROACH IN CANCER, A MINI REVIEW

Medicine

Christodoulou Panayiota	School of Medicine, European University Cyprus, Nicosia, Cyprus
Kyriakou Theodora-Christina	School of Medicine, European University Cyprus, Nicosia, Cyprus
Boutsikos Panagiotis	School of Medicine, European University Cyprus, Nicosia, Cyprus
Yiangos Lavranos	School of Medicine, European University Cyprus, Nicosia, Cyprus
Stephanou Anastasis	School of Medicine, European University Cyprus, Nicosia, Cyprus
Patrikios Ioannis*	School of Medicine, European University Cyprus, Nicosia, Cyprus *Corresponding Author

ABSTRACT

Research over the last four decades has provided convincing evidence supporting the preventive role of dietary agents including medicinal plants and herbs, against the risk of cancer. We now aim to identify natural phytochemical agents that can protect the normal cells (cytoprotection) from the toxic side-effects following chemotherapy treatment. Specific phytochemicals may exhibit chemopreventive abilities by suppressing key biomolecular signaling events during tumor initiation, promotion and progression. In this review, we summarize data regarding selective phytochemicals including Curcumin, Resveratrol, EGCG, Triptolide, Graviola (A. Muricata), Silymarin, Amygdalin (extract from apricots and peach kernels) and Chrysin, with emphasis on the evidence supporting the chemopreventive efficacy of these compounds in high-risk populations as well as their complex biomolecular mechanisms. Moreover, we are discussing how specific phytochemicals might be able to provide new horizons as chemopreventive agents of normal cells during chemotherapy; with potential positive results on protection from the severe adverse side-effects, thus contributing on improving the quality of life of patients.

KEYWORDS

Chemotherapy, cancer, chemoprevention, cytoprotection, phytochemicals, antioxidant, anti-cancer agents

INTRODUCTION

Cancer is one of the major causes of mortality and morbidity globally and still remains a compelling challenge for public health. It is characterized by uncontrolled growth and proliferation of cells that are able to travel through the bloodstream, invade and metastasize to the entire body (Serhani et al., 2019, Neophytou et al., 2018). Up to date, there are many types of cancer treatments and they vary depending on the type, location and extent of the disease. These treatments include surgery, chemotherapy, radiation therapy and immunotherapy.

Chemotherapy is one of the most effective and commonly used treatments in most types of malignancies. Chemotherapeutic drugs are well known to target cancer cells that are metastasized to different tissues of the body apart from the primary tumor. They are classified based on their mechanism of action as alkylating agents, platinum agents, antimetabolites, topoisomerase inhibitors, anti-microtubule agents, and antitumor antibiotics (Huang et al., 2017). However, despite their beneficial effect on cancer cells, conventional chemotherapeutic agents dangerously toxify (affect) normal cells and healthy body tissues, leading to dose-dependent side effects and secondary problems for the patient's, suggesting that chemotherapy is a non-selective process (Felici et al., 2002, Serhani et al., 2019, Scott, 1970, Kaestner and Sewell, 2007).These chemotherapeutic side effects mostly affect physical activity, quality of life and mental health(Scott, 1970) .Many of these drugs can cause toxicity, even at normal therapeutic dose. Myelosuppression is one of the most common toxicities of chemotherapy and leads to the significant clinical problem of thrombocytopenia (Vadhan-Raj, 2009). In addition, diarrhea, constipation, fatigue nausea and vomiting, peripheral neuropathy, infertility and cardiotoxicity are some of the most common side effects of chemotherapy (Cramp and Byron-Daniel, 2012, Cramp and Daniel, 2008, Bennett et al., 2016). Diarrhea and constipation are poorly understood toxicities and signs of alimentary mucositis, a condition that affects the gastrointestinal track (GI) (Gibson and Keefe, 2006, Stringer et al., 2009). Chemotherapy-induced peripheral neuropathy is associated with depression, ataxia and insomnia (Addington and Freimer, 2016). Infertility includes spermatogenesis and depends on the combination of drugs used and on the cumulate dose administered to the cancer patients (Brydoy et al., 2007, Dohle, 2010). Cardiotoxicity is induced by the production of free radicals that cause damage to cardiomyocytes, leading cardiomyopathy and even heart failure (Paulides and Wojnowski, 2007). All these side effects remain a major source of concern for both patients and clinicians despite the improved efficacy and advance efforts of cancer treatment(Nurgali et al., 2018). The limited efficacy of cancer treatment in several forms of cancer along with the adverse side effects and the disadvantages of cancer screening programs led to an increasing interest and attention in chemoprevention.

Chemoprevention is defined as the use of natural or synthetic non-essential dietary agents to stop the process of carcinogenesis and to prevent or delay tumor growth (Langner and Rzeski, 2012). This strategy has been expanded to target all three stages of cancer development, initiation, promotion and progression. In cancer initiation, it targets DNA repair, enzyme detoxification, ROS scavenging, and carcinogen metabolism while in cancer promotion and progression, it targets inhibition of cell proliferation, cell cycle arrest, induction of apoptosis, angiogenesis, differentiation and reduction of inflammation (Shu et al., 2010, Tsao et al., 2004). Dietary phytochemicals such as Curcumin, EGCG, Resveratrol, Sylimarin, Chrysin, Triptolide and A. Muricata, can induce chemo preventive effects in different types of cancer through specific signaling pathways (Johnson et al., 2011, Ganther, 1999). In the future, the combination of natural bioactive compounds with chemotherapeutic drugs could benefit anti-cancer efficacy and reduce side effects of chemotherapy.

CHEMOTHERAPEUTIC AGENTS

Alkylating agents

Alkylating agents are chemical molecules used in cancer treatment due to their ability to bind covalently to DNA strands and induce DNA damage. There are multiple subtypes of these agents such as nitrogen mustards (chlorambucil and cyclophosphamide), nitrosoureas (carmustine, lomustine and semustine), alkylsulfonates (busulfan), ethyleneimines (thiotepa), triazines (dacarbazine) and cisplatin (Zwelling et al., 1979, Damia and D'Incalci, 1998, Scott, 1970). They are mostly active in the resting phase of the cell and they attach an alkyl group to the guanine base of DNA nucleotides, at the 7th nitrogen atom of the purine ring (Povirk and Shuker, 1994). The mechanism of

alkylating agents to bind the DNA results to the blocking of DNA replication. However, as there is no specificity, side effects are appeared including myelosuppression, nausea and vomiting, and alopecia (D'Incalci and Sessa, 1997). Alkylating agents are teratogenic and leukemogenic, with secondary myelodysplasia and acuteleukemia.

Anti-metabolites

Anti-metabolites obstruct the building and replication of DNA leading to apoptosis. Their use in chemotherapy is quite common, as well as their combination with other drugs (Peters et al., 2000). They can be sub-classified as purine and pyrimidine antimetabolites and folic acid antagonists (Parker, 2009, Scott, 1970). They slow the synthesis of pyrimidine and purines that are used by the cells to build new DNA molecules in the S phase of cell cycle(Parker, 2009) . There are highly toxic causing side effects including dose-limiting myelosuppression, immunosuppression, pulmonary toxicity and severe neurotoxicity (Mihlon et al., 2010).

Antimicrotubule agents.

Anti-microtubule agents block cell growth by stopping mitotic division leading to apoptosis (Yue et al., 2010). Most microtubule targeting agents bind microtubules and impact tubulin stability:Vinca alkaloid site (destabilizing), taxane site (stabilizing), colchicine site (destabilizing) and laulimalide side (stabilizing)(Bates and Eastman, 2017).Vinca alkaloids examples areVincristine, Vinblastine and Vinorelbineand taxanes includepaclitaxel and docetaxel. Vinca alkaloids are the first widely used class of microtubule directed agents and are cell cycle-specific in the M phase, inhibit tubulin polymerization and prevent mitotic spindle formation (Mukhtar et al., 2014, Dumontet and Jordan, 2010). In contrast, the action of Taxanes is associated with microtubule stabilization rather than disruption (Singh et al., 2008, Altmann and Gertsch, 2007). Paclitaxel and Docetaxel bind to microtubules and enhance tubulin polymerization, leading to microtubule stabilization (Yue et al., 2010, Francis et al., 1995). Both Vinca alkaloids and Taxanes cause neurotoxicity in the form of sensory neuropathy.

Topoisomerase inhibitors.

Topoisomerases are enzymes that play crucial role in human cell homeostasis. They participate in vital biochemical processes such as synthesis and translation of DNA. Inhibition of these enzymes is a method of a therapeutic approach against cancer. More specifically, topoisomerase inhibitors are anticancer agents designed to interfere with the action of topoisomerase I and II (Li and Liu, 2001). They interfere with the processes of transcription and replication by causing DNA damage, induction of DNA replication, inhibition and failure to repair strand breaks; therefore, they lead to cell death. Examples of topoisomerase I inhibitors are Ironotecan and Topotecan which are derived from alkaloid camptothecin. Examples of topoisomerase II inhibitors are Doxorubicin, Etoposide and Mitoxantrone. Severe adverse effects cost by these drugs include myelosuppression, cardiotoxicity and mucositis.(Nitiss, 2009, Nitiss and Wang, 1996).

Antitumor antibiotics

Antitumor antibiotics are made from natural products and interfere with DNA inside the cells (Scott, 1970). These drugs act during multiple phases of cell cycle and are considered cell cycle specific. Despite their toxicity, their anti-carcinogenic action is one of the most profitably treatment against cancer. There are several types of these drugs including streptomycin, blemycin, daunorubicin, enediyne, doxorubicin, mitomycin C, actinomycin C, actinomycin D, mithramycin, pentostatin and other natural products. (Greentree, 1988, Minotti et al., 2004, Shao, 2008, Scott, 1970).

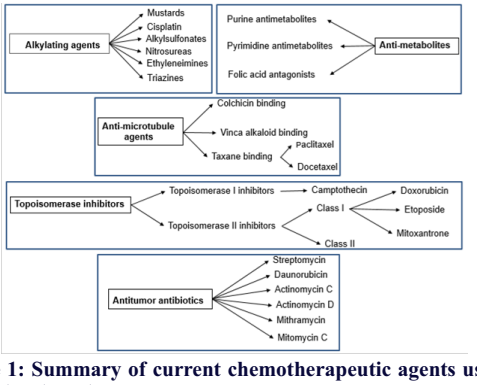

Figure 1: Summary of current chemotherapeutic agents used in cancer treatment.

MOLECULAR TARGETS OF CHEMOPREVENTIVE AGENTS

Chemoprevention corresponds mostly to a preventive treatment that involves the use of phytochemicals or natural bioactive compounds to prevent toxic side effects on the normal cells and promote therapeutic efficacy against the tumor cells. Up to date there is limited data regarding specific dietary phytochemicals as chemopreventive agents. We have already worked on one specific phytocompound annonacin as a good chemopreventive candidate (Yiallouri et. al 2018). Numerous *in vitro* and *in vivo* studies on specific phytochemicals have demonstrated that they have strong antioxidant, anti-inflammatory and anti-cancer activity by regulating specific signaling pathways and molecular markers in order to inhibit the occurrence and progression of cancer (Li et al., 2016, Priyadarsini and Nagini, 2012). In fact, phytochemicals have multiple molecular targets including reactive oxygen species (ROS) generation and signaling, xenobiotic-metabolizing enzymes, cyclooxygenase (COX-2) and lipoxygenase (LOX) pathways, transcription factors and proteins involved in cell cycle, apoptosis, invasion and metastases, and angiogenesis (Hun Lee et al., 2013, Kotecha et al., 2016, Yin et al., 2016).

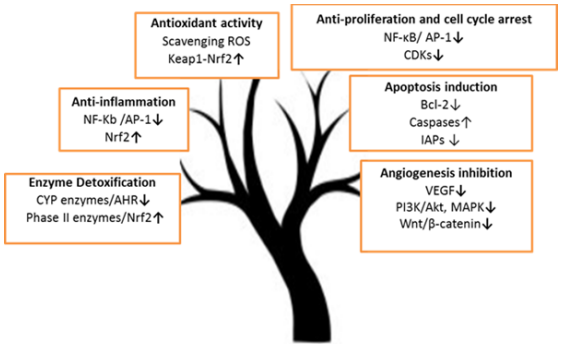

Figure 2: The molecular mechanisms targeted by phytochemicals in order to exert their chemopreventive effects: enzyme detoxification, anti-inflammation, antioxidant activity, anti-proliferation and cell cycle arrest, induction of apoptosis and inhibition of angiogenesis.

Carcinogen inactivation/ Detoxification of enzymes

DNA damage depends on the balance between carcinogen activation catalysed by phase I cytochrome P450 (CYP) enzymes, and detoxification achieved by phase II enzymes (Yin et al., 2016, Priyadarsini and Nagini, 2012). Aryl hydrocarbon hydroxylase receptor (AhR) is a ligand-activated transcription factor and when carcinogen binds to the receptor results in nuclear translocation and dimerization of AhR and induction of CYP enzymes. Phytochemicals such as Curcumin, EGCG and resveratrol exert their chemo preventive activity by damaging affecting nuclear translocation and dimerization of AhR, reducing the function of CYP enzymes while simultaneously increasing the activities of phase II enzymes through nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway(Li et al., 2016).

Antioxidant activity and anti-inflammatory effects

Oxidative stress occurs when reactive oxygen species (ROS) levels inside the cell become uncontrolled by exceeding the self- antioxidant capacity of the body (Priyadarsini and Nagini, 2012). The role of antioxidants is crucial during the development of cancer. Low levels of ROS are required for signal transduction while excessive levels can induce damage to all cellular components such as proteins, lipids, carbohydrates and nucleic acids(Priyadarsini and Nagini, 2012) . Excessive amount of ROS is known to play a key role in initiation, progression and development of various cancer types (Yin et al., 2016, Kotecha et al., 2016). Chronic inflammation that seems to be induced by oxidative stress is believed to be strongly associated with the main stages of carcinogenesis. As a carcinogenesis initiator, ROS contribute to the initiation of DNA mutations, generate DNA damage by producing oxidative modifications in cancer tissues and therefore, they lead to cancer cell proliferation and inhibition of apoptosis (Priyadarsini and Nagini, 2012, Li et al., 2016). Following the initiation stage, the ROS-induced promotion of malignant cell expansion is derived by regulating apoptosis-related genes and transcription factors such as NF-κB, Nrf2, AP-1 and HIF(Kotecha et al., 2016). The progression stage is non-reversible and includes the secretion of metastases-related proteases and invasion beyond the

instant primary tumor origin.

According to many clinical and preclinical studies, Nrf-2 activation has a key role in regulating the antioxidative stress response and is required for the anti-inflammatory response (Li et al., 2016, Yin et al., 2016). Many phytochemicals express their antioxidant activity and inhibit pro-inflammatory mediators COX-2 and LOX by damaging NF-κB and activator protein-1 (AP-1) and by inhibiting NO synthase induction. Nrf2 controls phase II detoxifying and antioxidant genes via binding to the antioxidant response element (ARE) region in the promoters of its target genes. Nrf2 regulated the genes for the proteins that regulate glutathione (GSH), antioxidant enzymes, drug metabolism enzymes and other stress response proteins (Li et al., 2016, Priyadarsini and Nagini, 2012, Yin et al., 2016). In several published research studies, it is denoted that Keap1-Nrf2 signal pathway mediates antioxidant and anti-inflammatory activity of phytochemicals in order to prevent cancer. Furthermore, Keap1-Nrf2 signaling pathway maintains redox balance and xenobiotic metabolism by inducing the expression of antioxidant and phase II detoxifying enzymes resulting in cellular defense against oxidative stress, and exert a cyto-protective mechanism. Functional interactions between Keap1-Nrf2 signaling pathway and NF-κB, AhR, p53, and NOTCH signaling pathways, induce Nrf2 to regulate and influence inflammation, tissue regeneration and metabolic reprogramming (Li et al., 2016).

Therefore, dietary phytochemicals show their anti-cancer effects through Keap1-Nrf2 pathway and they consist a source of evidence that antioxidants can prevent cellular damage induced by free ROS, suggesting that cancer may be slowed in the existence of increased levels of dietary endogenous or exogenous antioxidant supplements (Li et al., 2016, Yin et al., 2016).

Cell proliferation and cell cycle arrest

Excessive cell proliferation and impaired apoptosis are important factors for the development and progression of cancer. Dietary phytochemicals have been demonstrated to block cell proliferation by inhibiting signal transducing protein kinases and polyamine biosynthesis, induce cell cycle arrest at G0/G1 and G2/M checkpoints, upregulate inhibitors of cyclin-dependent kinases (CDKs), such as p21 and downregulate cyclins and CDKs (Priyadarsini and Nagini, 2012, Yin et al., 2016, Kasala et al., 2015a). Therefore, cell cycle stage and apoptosis play critical roles in the molecular pathogenesis of cancer and can affect the effectiveness of chemotherapy.

Apoptosis induction

Apoptosis can be divided into three non-distinct phases: an induction phase, effector phase, and a degradation phase (Kasala et al., 2015b, Yin et al., 2016, Priyadarsini and Nagini, 2012). The induction phase depends on death-inducing signaling to stimulate pro-apoptotic signal transduction cascades. Death-inducing signals include ROS, ceramide signaling, over activation of Ca^{2+} pathways, and Bcl-2 family proteins such as Bax and Bad (Priyadarsini and Nagini, 2012). The effector phase includes the commitment of cell to die by the action of mitochondrion. The last phase includes both cytoplasmic and nuclear events. The cytoplasmic events involve the activation of caspases and the nuclear events involve chromatin condensation, nuclear envelope breakdown and DNA fragmentation. At the end, the cell is fragmented into apoptotic bodies that are phagocytosed by surrounding cells or macrophages.

Phytochemicals induce apoptosis via activating death receptor signaling, altering expression of Bcl-2 family proteins that control mitochondrial release of cytochrome c, activating caspases and inducing downregulation of anti-apoptotic proteins (IAPs)(Yin et al., 2016) . In esophageal and pancreatic cancer cells, curcumin is well known for inducing apoptosis and cell cycle arrest by blocking Notch signaling pathways(Li et al., 2016, Kotecha et al., 2016). Blocking Notch signaling leads to downregulation of NFκB which in turn reduces the expression of target genes including IL-8, Bcl-2, cyclin D1 and vascular epithelial factor (Li et al., 2016). NF-κB is involved in the greater cell proliferation, invasion, angiogenesis, and suppression of apoptosis, metastasis and chemo-resistance in various types of cancer (Kotecha et al., 2016, Yin et al., 2016, Chung et al., 2013)

Angiogenesis inhibition

Angiogenesis is the growth of new blood vessels from existing vasculature. Unusual angiogenesis results in either poor vascularization or abnormal vasculature. Cancer cells or tumors promote uncontrolled angiogenesis able to be metastasized by the secretion of proangiogenic factors like VEGF (Priyadarsini and Nagini, 2012). Several in vitro and in vivo studies have showed that combination of curcumin and EGCG caused suppression of angiogenesis, cell proliferation and apoptosis induction, therefore synergistic growth inhibition of premalignant and malignant cells (Chung et al., 2013). Thus, all these molecular mechanisms show that phytochemicals might provide a novel therapeutic approach for cancer prevention but future clinical trials are required to confirm the specific preventive effect of phytochemicals on different cancer types (Li et al., 2016).

CANDIDATE CHEMOPREVENTIVE PHYTOCHEMICALS

In reality there is limited research discussing chemopreventive abilities or efficacy of any phytochemical. Most of the phytochemicals reported so far discuss their direct effects as anti-cancer agents. Thus, our lab is interested and working on specific phytochemicals as chemopreventive agents that are able to protect normal cells during the regimental chemotherapy procedure with known conventional drugs. We will also discuss specific candidate phytochemicals that have been showed to have anti-cancer properties that may also be promising candidates for chemoprevention and have cytoprotective properties in normal cells.

Curcumin

Curcumin, known as Curcuma longa or haldi in Hindi). is isolated from the roots of Curcuma longa (Zingiberaceae). It, is a phenylpropanoid that is formed from turmeric and it has been showed to be associated with strong anti-cancer properties (Ooko et al., 2017)It is also, a usual drug used in Ayurveda and TCM (define) in the treatment of diseases such as rheumatism, fever, intestinal disorders, trauma, and amenorrhea (Corson and Crews, 2007). Curcumin has been showed beneficial in all three stages of carcinogenesis. These effects are related to NFκb inhibition and therefore, induced anti-inflammatory, antioxidant and antitumor effects. It acts on multiple molecular targets to inhibit all stages of carcinogenesis including signaling pathway, cell cycle progression (cyclin D1), cell proliferation (EGFR), cell survival pathways (β-catenin), transcription factors (AP-1), metabolism related molecules (HIF-1), invasion and metastasis (CCL2 and MMPs), apoptosis related molecules (caspases and Bcl-2), and p53 upregulation(Chikara et al., 2018).

Resveratrol

The richest source of resveratrol is the roots of Polygonum cuspidatum (Ko-jo-kon), mainly cultivated in China and Japan (Yin et al., 2016). The skins of grapes contain about 50–100 mg/resveratrol, which seems to be responsible for the cardioprotective properties of red wine (Kotecha et al., 2016). During the last two decades, an increasing research interest has been expressed on the antioxidant, anti-inflammatory and anti-carcinogenic health benefits of resveratrol. It mediates its anticancer effects by regulating xenobiotic-metabolizing enzymes, inducing cell cycle arrest, inhibiting NO synthase, upregulating pro-apoptotic p53, Fas, and Bax, downregulating antiapoptotic proteins and inducing stimulating caspase activation. It inhibits NF-κb signaling by blocking IkB kinase activity and furthermore it suppresses VEGF and inhibits angiogenesis (Priyadarsini and Nagini, 2012).

Epigallocatechin-3-gallate (EGCG)

Epigallocatechin-3-gallate (EGCG), the most abundant catechin present in green tea, is mentioned as an important bioactive molecule responsible for many of the health influences of green tea, having anti-obesity and anti-diabetic properties (Mielgo-Ayuso et al., 2014). EGCG regulates several cellular signaling and metabolic pathways including inhibition of cancer cell growth, invasion, metastasis and induction of apoptosis in different cancer cells (Wu et al., 2019). In general, EGCG exerts anti-carcinogenic activities via inhibiting MAPK, AP-1 and cell transformation, and EGFR phosphorylation, it causes induction of cell cycle arrest (G0/G1) and inhibition of DNA methyl transferase activity (Chung et al., 2013).

Triptolide

Triptolide, is a epoxy diterpene monomer and is the main bioactive component of Tripterygium Wilfordii. In vitro and in vivo studies have shown strong activity of triptolide against mouse models of polycystic kidney disease (PKD) and pancreatic cancer, but its therapeutic potential remains unclear (Corson and Crews, 2007).

Triptolide induces calcium release by a polycystin (PC2) dependent mechanism. It inhibits cell proliferation and attenuates overall cyst formation by restoring Ca^{2+} signaling in autosomal dominant PKD cyst cells suggesting PC2-dependent Ca2+ release as a promising therapeutic strategy for ADPKD (Leuenroth et al., 2007). Triptolide has been shown to induce apoptosis and cell cycle arrest depending on its concentration and the cell type treated. However, basic cellular interactions and potential binding proteins involved in its mechanism have not been identified yet.

Annona Muricata

Annona Muricata is a lowland tropical fruit-bearing tree of the Annonaceae family and exists in the rainforests of South America, Africa and Southeast Asia. A. Muricata is commonly known as soursop, graviola, guanabana, or Brazilian pawpaw. The tree is low-branching, hairy and willowy, with leaves that appear soft dark green and the weight of the fruit varies from country to country (Moghadamtousi et al., 2015). A. Muricata is rich in flavonoids, isoquinoline alkaloids and annonaceous acetogenins (ACG). Graviola is well known for its anticancer activity and the active ACGs have shown that they can kill cancer cells that are resistant even to chemotherapeutic agents. The possible anticancer mechanisms of Graviola include induction of apoptosis by loss of MMP and activation of caspases, suppression of EGFR and JAK signaling leading to blockade of the PI3K, RAS and STAT pathways, respectively. This can result in decreasing cell viability, cell cycle arrest and metabolic failure by downregulating HIF-1A, GLUT1 and GLUT4 in human cancer cells. Graviola regulates inflammation by inhibiting NF-κB mediated TNF-a and IL-1, increases ROS generation via upregulation of enzyme systems such as catalases and it seems to kill drug resistant cells by regulating multidrug-resistant export proteins (Qazi et al., 2018). Therefore, numerous studies have reported that A.Muricata derived compounds are linked to a variety of anticancer effects including induction of apoptosis, cytotoxicity, anti-inflammatory activity and inhibition of proliferation and metastasis (Rady et al., 2018). In addition, there is an increasing interest that Graviola leave extract seems to promote selective cancer cell death through inhibiting sodium/potassium ATP and SERCA pumps, and future studies are required to show whether this approach can be considered as a dormant novel treatment for cancer (Yiallouris et al., 2018).

Amygdalin (extract from apricot and peach kernels)

Apricot and peaches provide reputable sources of vital vitamins. Studies have highlighted the positive effects of amygdalin, a cyanogenic compound found in both peach and apricot kernels, in its ability to suppress the development of cancer. The cyanogenic diglucoside has gained high popularity in cancer patients in combination with and in place of conventional therapy. Previous studies have showed that amygdalin's antitumor mechanism includes induction of apoptosis, inhibition of cell cycle related genes, and inhibition of cell proliferation (Song and Xu, 2014). However, there is not much about amygdalin and its benefit is controversial (Cassiem and de Kock, 2019). Daily intake due to increased therapeutic activity and low risk of toxicity may make these apricot and peach kernels in the future a viable chemopreventive angent (Cassiem and de Kock, 2019).

Silymarin

Silymarin, a flavonoid antioxidant isolated from seeds of milk thistle (Silybum marianum), shows high levels of chemoprotective activity by various antioxidant, anti-inflammatory, antiviral, immunomodulatory, proliferative, and metabolic effects; leading in various protective phenotypes, both in vitro and in vivo (Zi et al., 1998). It is one of the most widely used natural products for the treatment of hepatic diseases worldwide. It regulates imbalance between cell survival and cell death through interference with activity of cell cycle regulators and proteins involved in apoptosis. Silymarin also showed anti-inflammatory and anti-metastatic activity by modulating target proteins (Ramasamy and Agarwal, 2008). It inhibits EGFR signaling with downregulation of CDK expression and upregulation of the CDK inhibitors $p21^{CIP1}$ and $p27^{KIP1}$, with simultaneously increased binding to CDKs. Silymarin causes cell cycle arrest at the G1 and G2 checkpoints; in lower doses causes growth arrest by ERK1/2 inhibition while in higher doses leads to apoptosis by MAPK/JNK pathway. Concluding silymarin extract is now known as able to downregulate EGFR signaling through inhibiting expression and secretion of growth factors leading to impairment of downstream mitogenic events and therefore to an effective anticancer activity (Lovelace et al., 2015).

Chrysin

Chrysin is a natural polyphenolic component in the class of flavones that is mainly dominant in vegetables, fruits and nuts, with outstanding safety profile and smaller amount of toxicity. It has been lately attracted major attention in the field of chemoprevention. Chrysin is a hydroxylated flavone found in honey, propolis and other type of plants such as Pelargonium Crispum, Passiflora Incarnata, Oroxylum Indicum etc. (Salonen et al., 2017).

Nowadays, Chrysin is characterized by multiple bioactivities such us antioxidant, anti-inflammatory, antibacterial, anti-allergic, antidiabetic and anti-estrogenic activities. However, its antitumor potential is the most promising and is well validated for a variety of human cancer cell lines (Kasala et al., 2015b). It is demonstrated to induce cell cycle arrest and apoptosis through different mechanisms such as extrinsic apoptosis pathway activation, alteration of cyclins and CDKs. Furthermore, Chrysin modulates multiple signaling pathways including RAS-RAF-MAPKs, PI3K-Akt, STAT, NF-κB, wntc signaling/β-catenın and Notch signalling pathways ın order to ınhıbıt cell growth and prolıferatıon, angiogenesis, invasion and metastasis. Besides its anticancer properties as single agent, Chrysin was found to co-operate with various chemotherapeutic drugs including doxorubicin, cis-platin and ciglitazone to induce apoptosis and inhibition of tumor cell survival (Kasala et al., 2015b).

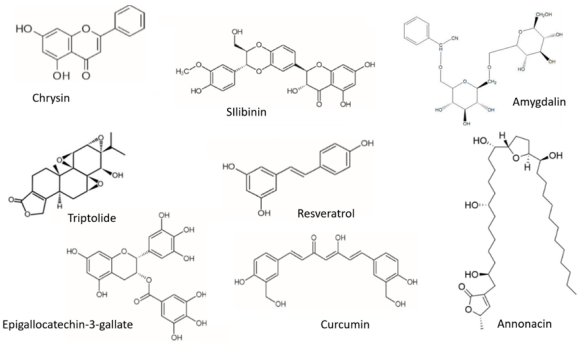

Figure 3: Natural products, the structure of the different chemopreventive phytochemicals

CONCLUDING REMARKS

Chemotherapy is one of the mainstream and first steps in cancer treatment in which patients are commonly suffering from various toxic side effects that affect a number of organs. Thus, strong and well tolerated chemopreventive agents that are able to protect organs, tissues and normal cells would be beneficial to the patient receiving chemotherapy. Phytochemicals exert their anticancer effect through multiple targets and signaling pathways that could block all stages of carcinogenesis including initiation, promotion and progression. Moreover, the ongoing problems of drug resistance, toxicity, and high treatment cost that are all associated with chemotherapy, suggests a need for alternative cancer treatments. Therefore it is of major importance to investigate other possible combinational treatment approaches such as phytochemicals together with chemotherapeutic drugs that are able to limit the toxicity of the drug but at the same time have synergistic effect in promoting cell death in cancer cells (Figure 4). We propose a beneficial effect of specific phytochemicals as anticancer as well as chemopreventive agents that might give us the opportunity to introduce novel therapeutic and chemopreventive interventions that might be safer, non-toxic, reliable, cheaper and without severe toxic side-effects; but at the same time promoting cytoprotective effects of normal cells during chemotherapy. We have recently reported that annonacin, the active phytochemical found in graviola seem to mediate its anti-cancer effects by inhibiting both Na+/K+ and SERCA AT Pase activity (Yiallouris et al. 2018). These findings might suggest that annonacin treatment can possibly sensitize those proteins promoting cell death. However, further studies are required to address the exact Biochemical pathways that allow phytochemicals to have selective death-promoting effects in cancer but at the same time have cytoprotective and chemopreventive

properties in normal cells following chemotherapy.

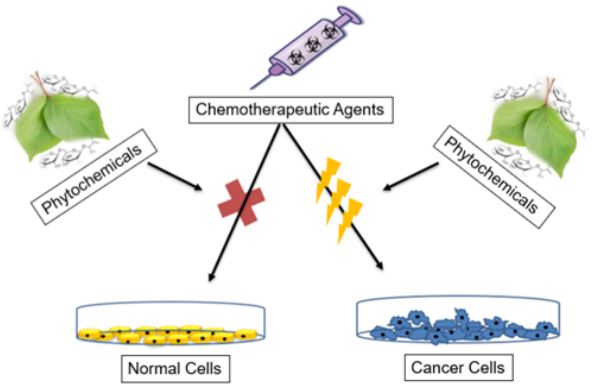

Figure 4: Schematic figure showing combinational treatment approach and chemopreventive targets of phytochemicals

"The authors declare that they have no competing interests"

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