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Review

Pharmacotherapeutic potential of phytochemicals: Implications in cancer chemoprevention and future perspectives

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ABSTRACT

Cancer is a leading cause of disease burden throughout the world. Many cancers develop as a result of exposure to both lifestyle and environmental factors that are potentially modifiable. In the last few years, much of the scientific attention has drawn to the discovery of new and effective chemopreventive agents from natural sources. A multitude of phytoconstituents have been explored for their potential to prevent the occurrence of carcinogenesis both *in vitro* and *in vivo* by means of diverse cellular and molecular approaches. Key focus of this review is to highlight some significant and new information about different molecular aspects of chemopreventive ability of plant based phytochemicals in terms of their inhibitory potential on cancer growth. In addition, information regarding certain limiting factors such as whole animal physiology, tumour microenvironment and bioavailability of active components of phytoconstituents used in pre/clinical trials are further explored. This review would further assist the scientific community involved in designing efficacious chemopreventive approaches using these phytochemicals in treating cancer.

1. Introduction

Cancer imposes great burden of disease worldwide due to its high incidence that leads to disability and premature mortality among humans [1]. In 2015, a total of 8.8 million deaths were due to cancer alone. This number is expected to rise by about 70 % over the next two decades. Cancers most frequently affecting men include prostate, lung, bronchus and colorectal whereas cancers of breast, lung and bronchus are more frequent in women. Breast cancer alone is expected to account for 29 % of all new cancer diagnoses in women [2]. High morbidity and mortality rate due to cancer has motivated huge scientific interest in discovery of newer anticancer agents from natural sources. There is an evidence that many cancers are caused by exposure to environmental and/or lifestyle factors while only a small proportion (up to 10 %) has been found to be due to inborn genetic defects [3,4]. There is strong relationship between excess reactive oxygen species (ROS) and onset of cancer *via* diverse metabolic processes [5]. ROS induced DNA instability can trigger many undesirable metabolic pathways which are critical in conversion of normal cells into malignant ones. Extremely reactive free radicals and their derivatives tend to react with DNA to form cross-links and adducts which results in base changes leading to mutations and initiation of cancer. Cancer progression ensues in multiple steps involving multiple signaling pathways and can be intervened at early steps [6]. Oxidative stress induced DNA injury, hepatic damage

Abbreviations: α-SMA, α-smooth muscle actin; AIF, apoptosis inducing factor; AP-1, activator protein 1; ARE, antioxidant response element; Bax, Bcl-2 associated X protein; Bcl-2, B-cell lymphoma 2; Bcl-xl, B cell lymphoma extra large; CDKCs, cyclin:CDK complexes; c-Myc, c-myelocytomatosis; c-JNK, phosphorylated c-Jun *N*-terminal kinase; COX-2, cyclooxygenase 2; DME, NAD dependent malic enzyme; EGFR, epidermal growth factor receptor; EpRE, electrophile response element; ERK, extracellular signal-regulated kinase; FADD, Fas associated death domain; FasL, Fas ligand; GAE, gallic acid equivalent; GP_X-1, glutathione peroxidase 1; GST, glutathione-*S*-transferase; HO-1, heme oxygenase 1; IKKβ, inhibitor of κB kinase β; iNOS, inducible nitric oxide synthase; JAK, Janus kinase; Keap1, Kelch-like ECH-associated protein 1; MAPKs, mitogen activated protein kinases; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor-κB; NQO1, NAD(P)H quinine dehydrogenase 1; Nrf2, nuclear factor erythroid 2 *p*45-related factor 2; PARP, poly ADP ribose polymerase; PGEs, prostaglandins; PI3K, phosphatidylinositol-3-kinase; PTEN, phophatase and tensin homolog; Raf, rapidly accelerated fibrosarcoma; Ras, retrovirus associated DNA sequences; Rb, retinoblastoma; RE, rutin equivalent; ROS, reactive oxygen species; SOD, superoxide dismutase; Src, sarcoma; STAT, signal transducer and activator of transcription; TGFβ1, tumour growth factor β1; TNF-α, tumour necrosis factor α; TRAIL, TNF related apoptosis inducing ligand; TSG, tumour suppressor gene; UGT, uridine diphosphate glucuronosyltransferase; VEGF, vascular endothelial growth factor

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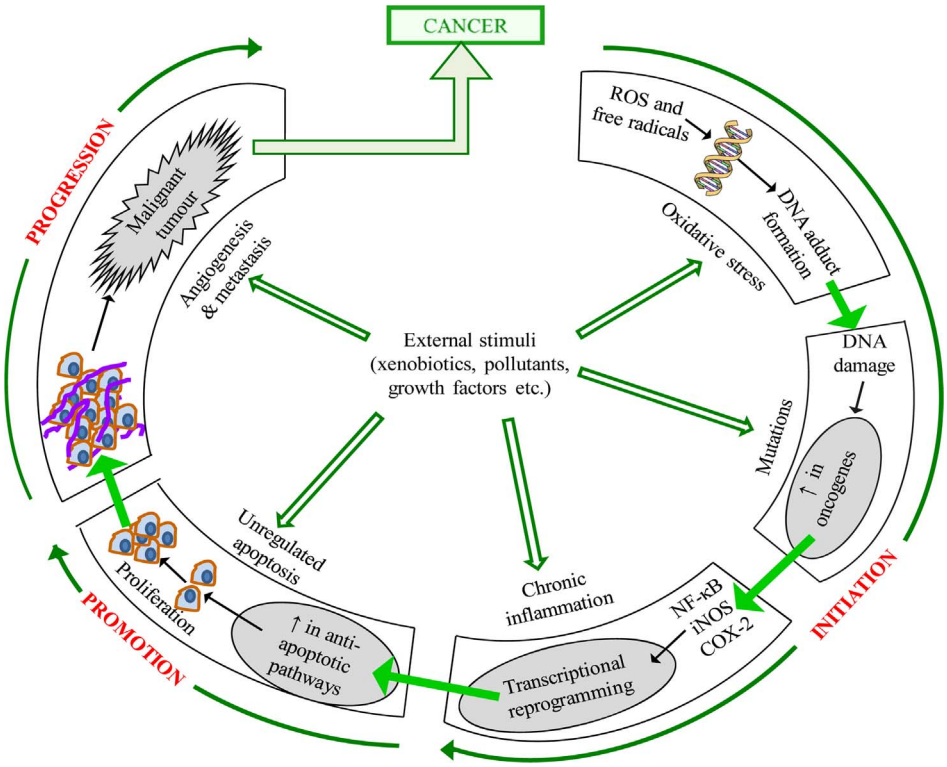

Fig. 1. Stages involved in the transformation of normal cells to cancerous state by various external stimuli for tumour initiation.
·OH: hydroxyl radical; iNOS: inducible nitric oxide synthase; COX-2: cyclooxygenase 2; NF-κB: nuclear factor κB; DNA: deoxyribonucleic acid; H_2O_2: hydrogen peroxide; CDKs: cyclin dependent kinases; $\cdot O_2^-$: superoxide radical.

due to xenobiotics and carcinogens, mutations in proto-oncogenes and tumour suppressor genes (TSGs), persistent inflammation, de-regulated apoptosis and uncontrolled cellular proliferation are believed to play an important role in cancer progression (Fig. 1). Plant based chemopreventive agents have been shown either to interrupt or end carcinogenesis at different levels. In Ayurvedic system of medicine, plant based preparations have been in use for hundreds of years in the form of traditional remedies [7,8]. Many dietary phytochemicals have potential to inhibit carcinogenic process by interfering with one or multiple cellular pathways and hence play an important role in cancer chemoprevention [9,10].

2. Cancer chemoprevention

Cancer chemoprevention can be explained as use of multiple intervention strategies by natural or synthetic agents to reverse, suppress or prevent the progression of carcinogenic process at various stages [11,12]. Many complications have been reported to be associated with conventional treatment approaches for treating cancer [13,14]. For instance, synthetic chemotherapeutic agents have adverse effects such as development of resistance to synthetic drugs in cancer cells, high price, continuing side effects etc. Furthermore, there are many phytochemicals which selectively act on cancer cells (Table 1). These may act on cancer cells or cancer stem cells (CSCs) that already have survived under stress conditions e.g. comparatively elevated ROS levels due to exaggerated metabolic activities which are under strict control in case of normal cells [15,16]. Administration of chemopreventive phytochemicals in small doses thus tends to affect only cancer cells and CSCs by further enhancing cellular stress thereby destroying them. Conversely, the changes induced by phytochemicals in normal cells can be tolerated without affecting their physiological response [17]. Many active natural compounds from medicinal plants have gained much attention in recent years that has been acknowledged by various scientific, epidemiological and pharmacological studies. This is mainly due to bio-active and chemopreventive properties including their anti-oxidative, anti-mutagenic/anti-genotoxic and anti-carcinogenic potential. These properties have further led to their use as a part of traditional medicines for management and treatment of many diseases including cancer thus targeting them as potential candidates for modern therapeutic approaches [18]. Importance of these chemopreventive properties of phytochemicals and medicinal plants can be evidenced by observing large number of publications on chemoprevention based upon bibliographic searches from PubMed over the last decade (Fig. 2). Phytochemicals are plants non-nutritive chemicals that are synthesized as a defense system in coping with harsh environmental stress conditions as well as many pathogens [19]. Presently, a vast amount of phytochemicals is being classified as terpenoids, polyphenols and alkaloids which contribute towards medicinal properties of plants and also form a part of human diet for nutraceutical purposes (Fig. 3). These metabolites are produced by plant systems largely *via* mevalonate and shikimate pathway wherein different primary metabolites function as their precursors [20].

3. Molecular targets of phytochemicals against carcinogenesis

Chemopreventive agents confer their protecting effects broadly by either hindering the formation of carcinogenic species or inhibiting the interaction of carcinogens with bio-molecules, predominantly DNA, hence acting as 'blocking agents'. In spite of this, certain mutations arise in genetic material which direct cells to reproduce even after damage. At this point, chemopreventive agents exhibit repressing effects, thus inhibiting further progression of transformed cells into tumour formation [9,21].

3.1. Anti-oxidant activity and scavenging of reactive oxygen species

One of the cornerstone strategies adapted by phytoconstituents for cancer prevention is offering anti-oxidant surroundings in normal cells to counterbalance lethal effects of oxidative stress. High levels of ROS and concurrent decline in cellular anti-oxidative defense induce oxidative stress that not only modulates some physiological pathways but also promotes development of cancer. Main culprits of oxidative stress are non-radical and radical centres e.g. hydrogen peroxide (H_2O_2), superoxide radical ($O_2\cdot^-$), hydroxyl radical (·OH), peroxyl radical (ROO