



## **Medical Biotechnology**

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Executive Editor



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# **Therapeutic, Health-Aiding and Tumor Suppressing Roles of Polyphenols**

### **Polyphenols Offering New Therapeutic Avenues to Battle Complex Diseases**

Polyphenols belong to a structural class of naturally occurring or synthetic/semisynthetic organic materials. They are versatile antioxidant compounds and offer medically and clinically important functional properties. The unique physical and chemical characteristics of polyphenols are due to their high molecular weights (500–4000) and phenolic substructures that consist of proteins and amino-based organics [1]. Previous studies have also shown that the formation of particular metal complexes, such as intense blue-black iron(III) complexes contribute to unique physical and chemical properties of polyphenols [1]. Resveratrol and flavanols, notably (-)-epicatechin are widely researched polyphenolic compounds [1, 2].

The ongoing research has revealed the potentials of polyphenols as extremely efficient drug agents that can be leveraged for new therapeutic designs for combating stroke related injuries, cancer and renal failures [1-3]. To this end, researchers have

shown that polyphenols could be ideal alternatives especially when co-administered with other drugs that are recommended for better efficacy and safety [3]. Lately, the naturally derived polyphenols that are plant and fruit derived secondary metabolites consisting of chemically contained benzene rings with OH moieties have emerged very promising for therapeutics [3, 4].

As new therapeutic applications are emerging, the family of polyphenols are getting extended from simple flavonoids and phenolic acids to structurally more complicated polyphenolic compounds including colored anthocyanins [5]. Such compounds are known to play important roles in the defense and protective mechanisms of plants [3]. Extensive research have been carried out on this chemical group of compounds covering both the extracts as well as the isolated compounds [3, 6]. Recent research conducted in these areas have indicated enormous potentials of these compounds exhibiting dynamic therapeutic and health aiding properties [3]. For example, natural resources of polyphenols including

green tea, almond, and berries have demonstrated beneficial and pharmacological activities in prevention of neurodegeneration, aging, tumorigenesis, and metabolic disorders and also diabetes. In

addition, the application of polyphenol has also shown beneficial activity in the treatment of pathogen infection, hypertension, and cardiovascular diseases (Figure 1) [3].

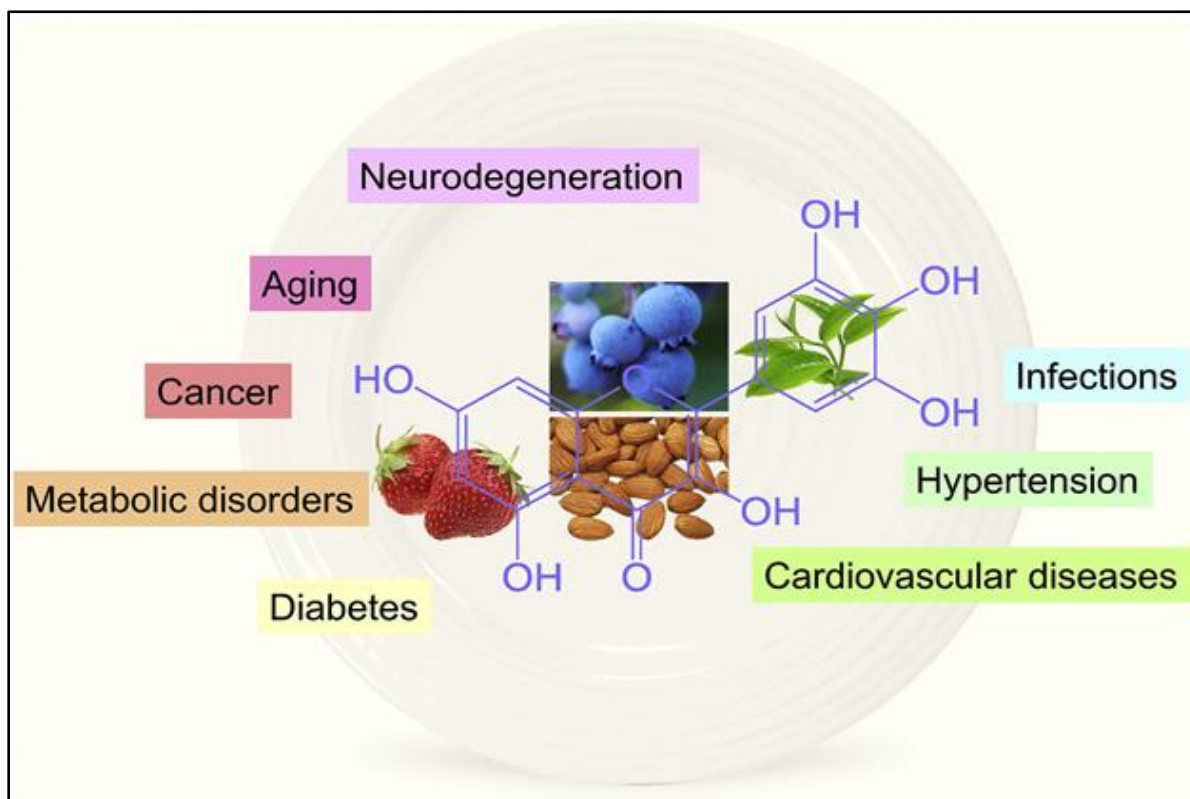


Figure 1: Versatile applications of polyphenols that exhibit high therapeutic potential in various complex diseases and medical conditions [Source: *Biotechnology Advances* (2020)].

### The Potential Anti-Cancer Activity of Polyphenols

Researchers have shown numerous signaling pathways including the death receptor (extrinsic) pathway, the mitochondrial (intrinsic) pathway and the perforin-granzyme apoptotic pathway through which polyphenols are believed to carry out potential anticancer activity [3, 7]. Especially, investigations on the p53 signaling pathway have suggested its significant contributions in cell cycle

regulation, metabolism, aging and development, reproduction, and suppression of tumor expression [3]. Polyphenols were shown to use p53 signaling pathway to produce anticancer activity through apoptosis in variety of cancers [3]. However, it is also of concern that several genomic studies have revealed that p53 frequently encounter mutation in different cancer cell lines, which can compromise its functional role [3].

### The Possibility of Polyphenols Modulating p53 Signaling Pathways

The p53 protein that is encoded in humans by the tumor suppressor 53 (TP53) gene is known to be located on the short arm of chromosome 17 [3]. The important role of P53 is defined by its activity as a sequence-specific nuclear transcription factor that binds to defined sites within the DNA. Subsequently, it negatively regulates transcription of genes that controls cell cycle progression DNA repair, metabolism, senescence, cell death, and angiogenesis [8].

Various studies have demonstrated multiple mechanisms such as induction of

apoptosis, regulation of various signaling pathways, regulation of cell cycle, and activation of receptors at the level of plasma membrane as the important factors of anti-carcinogenic effects of polyphenols [3]. In this regard, research studies have indicated the anticancer effects of polyphenols due to their ability to modulate glucose uptake and metabolism in various cancer cells [3]. It has been shown that the overexpression of p53 protein can be induced by a number of polyphenolic compounds such as resveratrol, curcumin and epigallocatechin-3-gallate [1, 3].

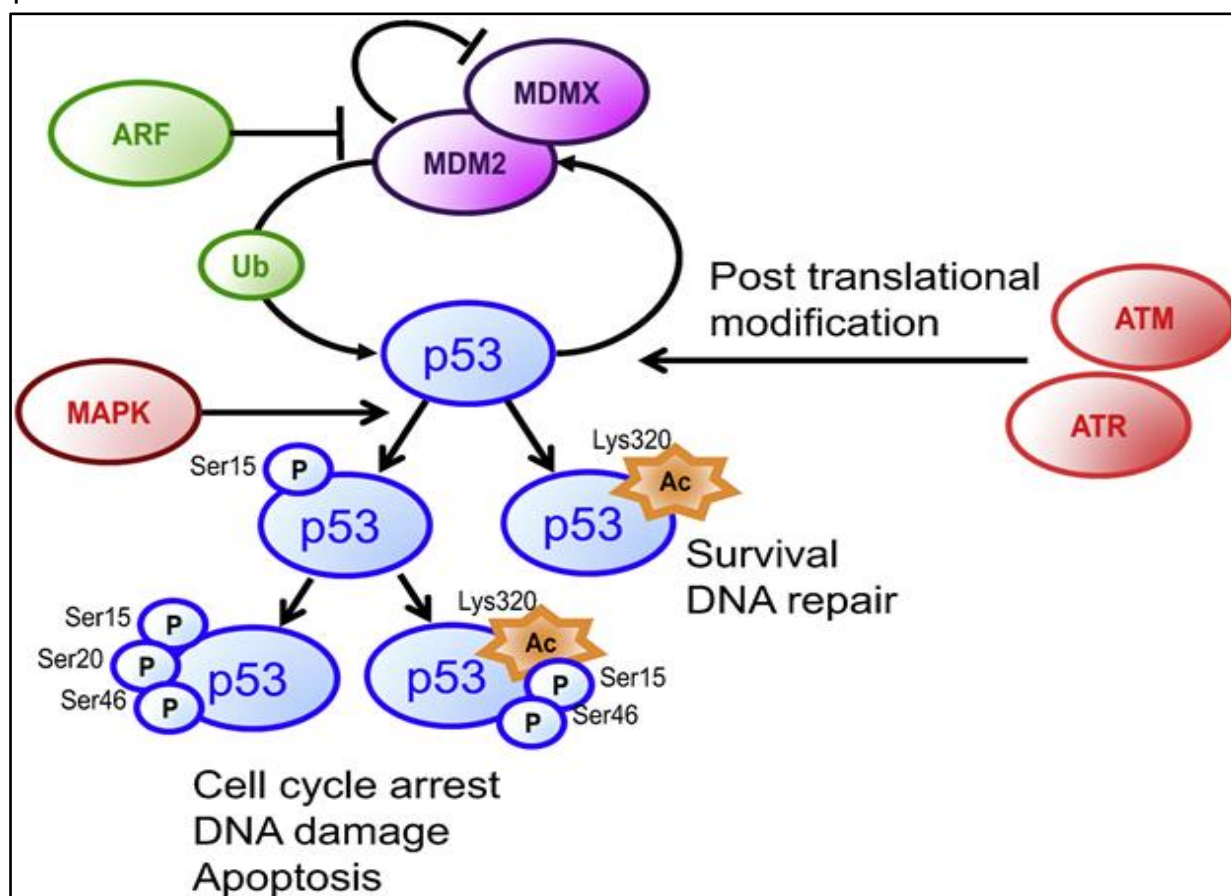


Figure 2: Polyphenols can induce various post-translational modifications of p53 that eventually control the function of p53. Ac, acetylation; P, phosphorylation; Ub, ubiquitination [Source: Biotechnology Advances (2020)].

In this connection, it has been observed that polyphenols like genistein, luteolin, quercetin, and wogonin that are abundantly in grapes, black and green tea or berry-derived products can account for its upregulation expression of p53 protein [3]. To this end, researchers have shown the ability of MDM2 and MDMX protein to regulate the stability of p53 through ubiquitination. Further, studies have indicated that phosphorylation of p53 at different serine residues can lead to cell cycle arrest, DNA damage, and apoptotic cell death. This occurs together with acetylation at lysine residue that tune the function of p53 in cell survival and DNA repair (Figure 2) [3].

Researchers employed assays for the activities of resveratrol and black tea polyphenols separately and also their combined forms in a mouse model of skin tumors. They showed that treatments significantly reduced the tumor incidence and volume. The mechanism of action was thought to be the raise in phosphorylated p53, the inhibition of MAPKs signaling and the induction of apoptosis [3].

### **Pre-Clinical Trials of Polyphenols for Cancer Prevention**

In view of the promising results for cancer prevention, current R&D has focused on clinical trials of polyphenols including curcumin, genistein and Broccoli Sprout that contain sulforaphane and polyphenols containing sulforaphane and polyphenols [3]. Lately, the application of new technologies such as bionanotechnology have shown for different therapeutic modifications that have been employed improve the solubility, biocompatibility and bioavailability of polyphenols [9]. In this regard, researches

included new design of dynamic drug carrier systems for specific targeting and encapsulation techniques [3]. In a significant study, naringenin was shown to be a promising candidate for treatment of hepatocarcinogenesis. This study reported naringenin inhibiting cell proliferation that induced apoptosis cell death in human hepatocellular carcinoma [10]. In another pre-clinical study, quercetin was shown to arrest S phase in human breast cancer cells by increasing p53 and p57 proteins [3].

### **Concluding Remarks**

The ongoing research on the natural polyphenols has shown tremendous promise for polyphenols to be an alternative therapeutic agent that is more effective and less toxic. Researchers have shown the anticancer effects of polyphenols that are attributed to several signaling pathways including the tumor suppressor gene tumor p53 protein. Several polyphenolic compounds can be derived from a wide variety of dietary sources including curcumin, resveratrol, genistein, luteolin, quercetin, wogonin and epigallocatechin-3-gallate. Studies have strongly suggested that these compounds can potentially upregulate p53 expression in several cancer cell lines through distinct mechanisms of action. Further, it has been shown that polyphenols can stabilize p53 protein through p53 phosphorylation, p53 acetylation and reduction of oxidative stress. We anticipate more in-vitro and in-vivo studies of polyphenols for their promising anticancer effects would be undertaken in the future that would involve modulation of p53 signaling pathways.

## References for Further Reading

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