1. Introduction
Phenolic compounds, found abundantly in various parts of the plant, are known to have key roles in combating various diseases associated with oxidative stress such as cancer, diabetes and cardiovascular complications (1). These phytochemicals range from low molecular weight, single aromatic ringed compounds to high molecular weight large complex polyphenols. Prior studies have demonstrated that the health beneficial effects of dietary phenols are due to their ability to exhibit antioxidant, anti-inflammatory and anticancer activities (2). Plant phenolic acids form an integral part of our diet and thus making them a prime focus of interest. For example, cereals, legumes, soybeans, coffee, tea, rosemary and thyme, which are widely utilized in diet, are the rich sources of phenolic acids (3). Fruits from berry and citrus family members, apples and pears have also known to contain considerable amounts of phenolic acids (4). Owing to their antioxidant capacities that include free radical scavenging activity, metal chelating activity and anti-proliferative potential there has been an increased interest in developing diets rich in plant derived polyphenols. These activities are found to be much essential for preventing cancer, atherosclerosis and neurodegenerative disorders (5).

More than 8000 natural phenolic compounds have been identified to date (6). Phenylalanine and/or tyrosine are the major precursors for the synthesis of phenolic acids through shikimate pathway (7). Addition of hydroxyl groups into the phenyl ring is the key step involved in the biosynthesis of phenolic acids (7) (Figure-1).

**Figure 1: Biosynthetic pathway of plant phenolic acids.** The phosphoenolpyruvate react with erythrose-4-phosphate to give chorismic acid, which is a precursor for tyrosine and phenylalanine. Phenylalanine serves as precursors for cinnamic acid derivatives. However, benzoic acids are synthesized from iso chorismic acid via oxidative and non-oxidative pathways.
a. **Classification of plant phenolics**
Phenolic acids that range from low molecular weight single aromatic ring structure to high molecular weight polymeric compounds are broadly classified into simple and complex phenolics (Figure-2).

![Figure 2: Classification of Phenolic compounds](image)

**Figure 2: Classification of Phenolic compounds**: Figure 2 shows the classification of plant phenolics based on their structure. Broadly plant phenolic compounds are classified as simple and complex phenolic acids. Simple phenolic acids are further classified as benzoic and cinnamic acid derivatives while complex phenolic acids are classified as flavonoids, tannins and stilbenes.

b. **Simple Phenolics**
Benzoic acids (BA) and cinnamic acids (CA) are the most simple phenolic acids found in nature with 6- and 9- carbon skeletons (8). These compounds contain a carboxylic group attached to the benzene ring with one or more hydroxyl or methoxyl groups attached (9). For example, gallic acid has three hydroxy (-OH) groups attached at 3\(^{rd}\) (meta), 4\(^{th}\) (para) and 5\(^{th}\) (meta) carbon, whereas the syringic acid contain two methoxy (-OCH\(_3\)) groups at 3\(^{rd}\) and 5\(^{th}\) (meta) and one -OH group at 4\(^{th}\) carbon (para) (10). The cinnamic acids in addition, have a propionic acid side chain attached to the benzene ring (11). Caffeic acid contains two -OH groups at 3\(^{rd}\) and 4\(^{th}\) carbon while Ferulic acid has one -OCH\(_3\) and one -OH group attached at 3\(^{rd}\) and 4\(^{th}\) carbon atoms respectively. (Figure 3)
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Figure 3: Structures of simple phenolic acids commonly found in nature: Benzoic acid derivatives have a carboxylic acid side chain attached to benzene ring while cinnamic acids contain a propionic acid side chain attached to the benzene ring. The most commonly found BA derivative; Gallic acid contains 3-OH groups attached at 3rd (meta), 4th (para) and 5th (meta) carbon atoms, whereas the syringic acid contain two methoxy (-OCH₃) groups [one at 3rd and the other at 5th (meta) position] and one -OH group at 4th carbon (para). Caffeic acid contains two -OH groups one at 3rd position and the other at 4th position, while Ferulic acid has one -OCH₃ and one -OH group attached at 3rd and 4th carbon atoms respectively.

c. Complex Phenolics
Complex phenolics are compounds with higher molecular weight, which are commonly found in the cell vacuoles (12). Tannins, the condensed tannins, flavonoids are few complex phenolics found among fruits and vegetables (4).
Flavonoids are made up of 2 phenolic rings to which an oxygenated heterocyclic pyran ring is attached (13). The oxygenated status of the pyran ring further classifies flavonoids into several groups that include: anthocyanins, flavones, flavanols etc. Higher complexity is achieved due to the acetylation or glycosylation of these molecules beyond their primary substitutions with hydroxyl or methoxyl groups (14) (Figure-4)
Figure 4: Structures of complex phenolic acids found in nature:
Flavonoids including Flavanols, flavanone, Flavone, isoflavone and anthocyanins are few complex phenolic acids found in nature

d. Benzoic and Cinnamic acid derivatives
Benzoic (BA) and cinnamic acid (CA) derivatives are commonly found in fruits and vegetables. Gallic acid, protocatechuic acid, vanillic acid are few among the several benzoic acid derivatives (15-17) while caffeic acid, ferulic acid, sinapic acid, caffeic acid phenyl esters (CAPE) are the commonly found cinnamic acid derivatives (18). These BA and CA derivatives are widely distributed among various parts of the plants including roots, leaves, fruits and vegetables (19). Caffeic acid is the most common type of phenolic acid found widely in the fruits, while the ferulic acid is found in the cell walls of seed coat, bran and fruits in esterified form (20). A study has shown that gallic acid is the most common phenolic acid found among fruits, vegetables, chestnuts and green chicory (21).
While a separate study by Kivilompolo M 2007 et al., reported that herbs like thyme, oregano and sage are rich in caffeic acids (22). These phenolic acids are well known for their free radical scavenging activities, hence considered as potent molecules that could be used for the treatment of diseases originating from oxidative stress. The radical scavenging activity of these molecules is attributed to the hydrogen or electron donating abilities that results in the stabilization of the phenoxy radicals (23). In addition they are
also well known chelators of metal ions such as copper and iron which serves as catalyst for oxidative stress and modulating ARE/NRF-2 pathways (23). The free radical scavenging activity, antioxidant, and pro-oxidant characteristics are primarily responsible for the antitumor activities of phenolic compounds (24).

e. SAR Studies
The molecular structure of the phenolic compounds, more precisely the number and position of hydroxyl groups and the double bond determine their pharmacological properties (25). Substitution of the active groups such as OH, OCH3, NH2, halogens in the ortho positions was found to be more active when compared to para and meta positions due to their ability to form intramolecular hydrogen bonding (25). In addition, the presence of phenolic group and the capacity of the compound to stabilize the resulting phenoxy radicals also contribute to their activity (23). Caffeic acid derivatives with ester or amide side chain have higher radical scavenging activities and lower redox potentials than caffeic acid itself, while the alkyl derivatives of ferulic and sinapic acid had lower antioxidant activities. The results thus can be concluded that the effect of side chain is related to number of hydroxyl groups and the aromatic substitution pattern (23). Differences in the antioxidant activity of ferulic acid derivatives were observed due to the presence of characteristic groups (-COOH, -CHO, -CH2OH, -CH3, and -COOC2H5) at the end of their carbon side chains (26). Among the cinnamic acid derivatives the radical scavenging activity of caffeic acid was found to be better followed by sinapic acid, ferulic acid and coumaric acid (27). The anticancer activity of benzoic and cinnamic acid derivatives is primarily due to the presence of the catechol ring and conjugated double bonds and partly due to its antioxidant mechanisms (28). Esters of cinnamic acids are more potent when compared to the hydroxylated or the methoxylated versions (28). Among the 20 different caffeic acid analogues, 4-phenylbutyl caffeate, (Z)-8-phenyl-7-octenyl and (E)-8-phenyl-7-octenyl caffeate exhibited potent anti-tumor activity with EC50 value of 0.02 μM (29).

f. Mechanism of action
Reactive oxygen species are continuously synthesized as byproducts by mitochondrial respiratory chain. ROS serves as second messengers in cell signaling pathways thereby control cell proliferation, differentiation and angiogenesis (30). Slight increase in the ROS levels is suppressed by the antioxidants present in the cells. Under certain conditions the levels of ROS exceeds the antioxidant defense capacity leading to oxidative stress. Gallic acid, a benzoic acid derivative induces protection to cells against the oxidative damage caused by the reactive oxygen species such as hydroxyl (HO•), superoxide (O2•−), and peroxyl (ROO•) and the non-radicals, hydrogen peroxide (H2O2) and hypochlorous acid (HOCl) making it as a good antioxidant. However, at lower concentrations and in the presence of metal chelators, gallic acid acts as a pro-oxidant thereby help in selective killing of cancer cells by enhancing cellular ROS levels. Due to the altered levels of antioxidant enzymes, the cancer cells become incapable of defending themselves leading to death (31). Protocatechuic acid exerts antioxidant activity either by scavenging the free radicals by donating hydrogen atom (H•) or electron (e). Caffeic acid and ferulic acids, a cinnamic acid derivative, inhibit membrane lipid peroxidation by chelating the metal ions as well as by acting as hydrogen donor, thus preventing the deleterious effects of peroxyl and alkoxy radicals (32, 33). In addition, benzoic acid derivatives, hydroxybenzoic acids and protocatechuic acid have been reported to exhibit dose dependent cytotoxicity on prostate (PC-3) and breast (MCF-7) cancer cells (34). Mechanistically, 4-hydroxy benzoic acid inhibited the histone
deacetylase enzyme thus modifying the acetylation process thereby inducing the cancer cell death (35). Protocatechuic acid targets the RhoB activation leading to decreased MMP thus inhibiting the cancer cell migration (17). These compounds induce apoptosis, and enhance lactate dehydrogenase levels by reducing the mitochondrial membrane potential. In addition, these compounds trigger the fragmentation of DNA in breast, lung, liver and prostate cancer cell lines (36). Similarly, gallic acid inhibits the cancer cell proliferation by promoting the generation of reactive oxygen species and arresting cells in G2/M phase (37). Thus benzoic acid derivatives could be promising anticancer compounds. Cinnamic acid derivatives CAPE - caffeic acid phenyl ester and Caffeic acid are well known antioxidants, reported to modulate key signaling pathways such as NF-kB, MAPK and AKT (38). Furthermore, CAPE and CAA induced cell death via apoptosis and cell cycle arrest in cell lines representing carcinomas of oral cavity, neck and tongue (28, 39, 40). In addition, CAPE is known to inhibit the nuclear factor kappa-light chain enhancer of activated B cells i.e NF-kB, which further enhanced the expression levels of p21, p53 (41). P-Coumaric acid, an abundant isomer of cinnamic acid, inhibits the colon cancer cell lines by increasing the ROS levels, decreasing the mitochondrial membrane potential and inhibiting the cell cycle at sub G1 phase. Although these phenolic acids are good antioxidants, they behave as prooxidants also in the cell system thereby increasing the radical generation, thereby killing cancer cells. In addition they target several key signaling pathways which leads to inhibition of cancer cell proliferation.