

**Review**

## **Nutraceutical Horticulture : An overview of biochemical and molecular considerations**

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The major components of our diet, namely, carbohydrates, fats, proteins, vitamins, and minerals provide for the building blocks besides serving as metabolic fuel to fulfil the bioenergetic needs. Since they serve the basic cellular needs, they are considered as ‘primary metabolites’. The molecular and biochemical pathways modulated by the major food components of our diet are well-established. Many phytochemicals referred to as ‘secondary metabolites’ and not considered as an ‘essential part’ of our diet, also find their way into the digestive tract along with the major food components. Interest in the role played by the ‘non-essential’ or ‘minor’ components of our diet in preventing the initiation or progression of metabolic disorders has gained momentum. The metabolic disorders, by and large, are non-pathogenic in nature and originate as a consequence of derailed cellular metabolism.

Plants produce over 50,000 phytochemicals belonging to the major groups of secondary metabolites such as phenolics, alkaloids, saponins and terpenes. The secondary metabolites serve several functions in plants and tend to accumulate in various plant parts in response to biotic and/or abiotic interactions. Many of the secondary metabolites are used by the pharmaceutical industry either in the formulation drugs directly, or as precursors for active ingredients in the drug formulations.

The secondary metabolites associated with our diet are known to influence cellular function upon assimilation. Such dietary phytochemicals capable of sustaining normal cellular function and sustain health are known as ‘nutraceuticals’. Although phytochemicals of nutraceutical value occur widely, horticultural crops such as fruits, vegetables and spices are particularly rich in nutraceuticals. The interest in the nutraceuticals is on the increase as

can be ascertained from number of books and journals featuring research articles on nutraceuticals (Fig. 1, 2). This talk will focus on the role of dietary nutraceuticals derived from fruits, vegetables, and spices in sustaining health *via* their interaction with the biochemical/molecular components in our cells.

### **Cellular components interacting with nutraceuticals**

The biochemical pathways modulated by the dietary nutraceuticals are many and complex. However, the major player interacting with nutraceuticals appears to be the nuclear transcription factor (NF-KB). Many dietary nutraceuticals exhibit inhibitory effect on NF-kB (Fig. 3). In addition, nutraceuticals are capable of inhibiting NF-kB activation mediated by the tumor necrosis factor-alpha (TNF- $\alpha$ ), a cell-signaling molecule. The activation of NF-kB transcribes genes that mediate the initiation and progression of several metabolic disorders.

### **Transcription factors**

Transcription factors are proteins that bind to DNA to effect transcription. Over 1600 transcription factors exist in mammalian cells. One such transcription factor of importance is NF-kB. As many as 133, 517 citations (Oct 2021; PubMed Central, National Center for Biotechnology Information, NCBI) exist on various aspects of NF-kB. It is a transcription factor of relevance to the initiation and progression of diseases. Therefore, inhibition of NF-kB and/or its endogenous activators (see below) are considered valuable targets for drug development.

NF-kB was discovered in 1986 by Ranjan Sen and David Baltimore. It is ubiquitous to all mammalian cells and exists in the cytoplasm. NF-kB is expressed constitutively and remains inactive when



bound to its inhibitory peptide, I $\kappa$ B $\alpha$ . The list of activators of NF- $\kappa$ B is large and include biotic as well as abiotic factors such as viral antigens, free-radicals (FRs), carcinogens, environmental pollutants, alcohol, to name a few. In addition, a family of endogenous peptides known as tumor necrosis factors (TNFs), play a crucial role in the activation of NF- $\kappa$ B. Upon binding to its activators, TNF promotes degradation of its inhibitory peptide (I $\kappa$ B $\alpha$ ) resulting in the activation of NF- $\kappa$ B. The active NF- $\kappa$ B then enters the nucleus and binds to the response elements (RE) of DNA to promote transcription. In fact, active NF- $\kappa$ B has potential to transcribe over 150 genes with a potential to deregulate cellular function.

### **Tumor Necrosis Factor**

TNF is a transmembrane protein that plays a crucial role in the activation of NF- $\kappa$ B. It was first isolated in 1984 and identified as an endogenous tumor regression factor. Therefore, it was designated as a tumor necrosis factor. However, over the years, the TNF was identified as a pro-inflammatory cytokine (cell-signaling peptide) with an ability to initiate several inflammation-induced metabolic disorders upon binding to its elicitors. Thus, TNF has a dual role in cell metabolism and often described as a ‘double-edged sword’. The localized and controlled expression of TNF-mediated inflammatory reaction has therapeutic significance. However, its uncontrolled expression leads to chronic inflammation and contribute toward metabolic disorders. For example, in cancer cells, TNF is expressed constitutively. TNF plays a crucial role in pathogenesis of several diseases and hence has attracted a greater research interest. Several synthetic FDA approved drugs as inhibitors of TNF are currently available. The TNF inhibitor drug industry is expected to reach 42.1 billion US \$ in the year 2025.

### **Biochemical/molecular pathways modulated by the active TNF and NF- $\kappa$ B**

As described above, activation of TNF and NF- $\kappa$ B has potential to result in far-reaching consequences through their abilities in initiating transcriptions detrimental to the normal cellular function. Such transcriptional changes are significant to derail cells from their normal function by activating pro-inflammatory pathways. Although localized and

regulated inflammation is beneficial in containing the disease progression, chronic inflammation contributes toward a number of diseases. In fact, most disease names ending with suffix “*itis*” (bronchitis, hepatitis, meningitis...) suggest inflammatory origin (*itis*: inflammation).

By inhibiting apoptosis (programmed cell death) and promoting angiogenesis (development of new blood vessels), NF- $\kappa$ B confers immortality to abnormal cells. Factors that inhibit apoptosis promote proliferation of cells with undesirable function. NF- $\kappa$ B also promotes development of new blood vessels (angiogenesis). Among several factors that promote angiogenesis, vesicular endothelial growth factor (VEGF) plays a major role in the development of blood vessels. Developing tumor cells promote angiogenesis mediated by VEGF. Inhibition of angiogenesis is therefore desirable for containing tumor growth. To date, over 14 FDA approved angiogenesis inhibitors are available.

### **Inhibition of TNF, NF- $\kappa$ B and associated cellular events by nutraceuticals from fruits, vegetables, and spices**

By their ability to inhibit activation of TNF and NF- $\kappa$ B, nutraceuticals derived from fruits, vegetables, and spices modulate inflammation, apoptosis, and angiogenesis (Fig. 2, 3). These molecular/biochemical events promote metabolic disorders such as cancer. A significant body of knowledge exists pertaining to the potential and mode of action of nutraceuticals in containing diseases such as prostate, breast, colon cancer and Alzheimer’s disease. To date, information pertaining to the nutraceutical benefits of curcumin (turmeric), quercetin (onion), resveratrol (red grapes, peanut seed coat), sulforaphane (cole crops) and capsaicin (chilies) appear prominently (Fig. 4abc and 5ab). It is evident from the published literature that studies on the nutraceutical benefits of other horticultural crops are actively pursued.

An interdisciplinary course covering the nutraceutical aspects of horticultural crops will be a very useful addition to the undergraduate or graduate curriculum. Such a course deriving appropriate content from horticulture, biochemistry, molecular biology, food science, pharmacology, and human physiology will be valuable to advance awareness on the scientific basis for the health sustaining benefits of fruits, vegetables, and spices.

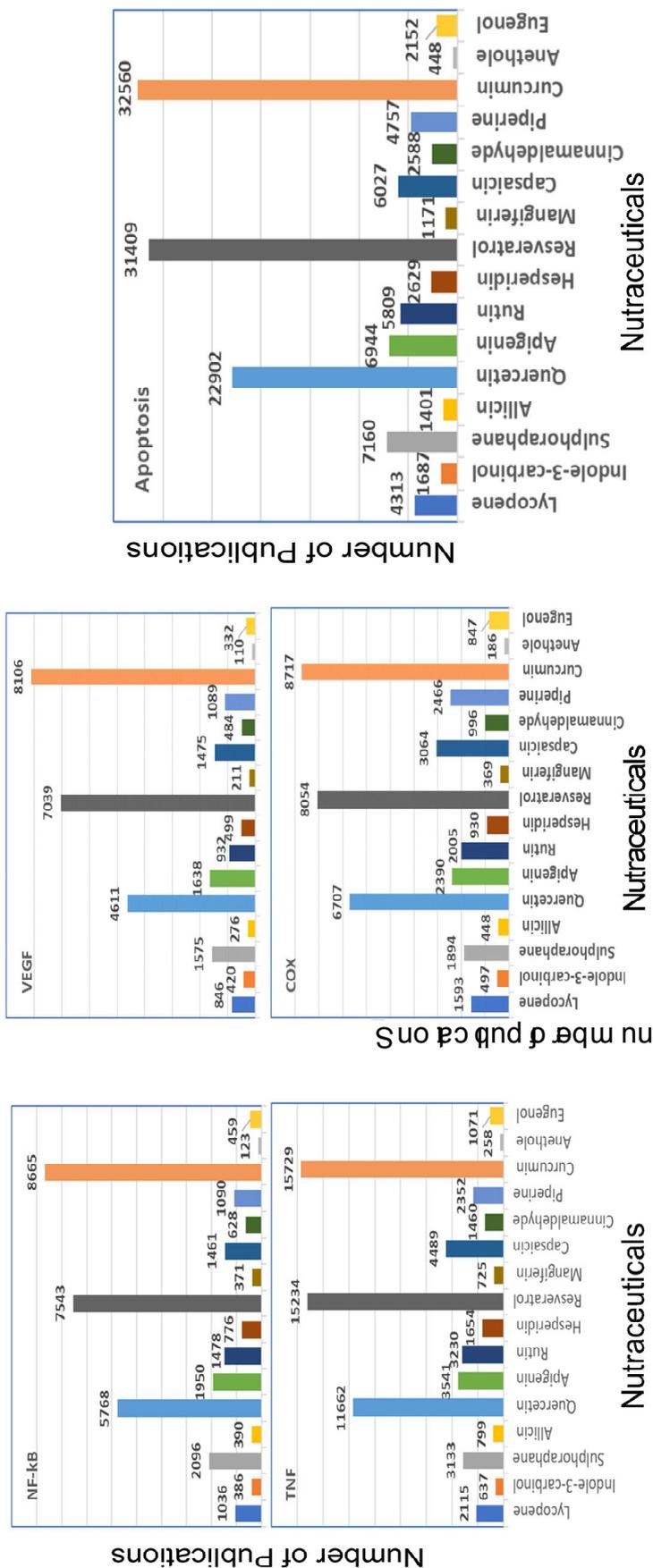


Fig. 1. Number of publications pertaining to the nutraceutical phytochemicals of selected fruits, vegetables and spices capable modulating inflammation, apoptosis (programmed cell death) and angiogenesis by their ability to inhibit activation of TNF (tumor necrosis factor) and NF-kB (nuclear transcription factor). *Source:* National Center for Biotechnology Information, USA.

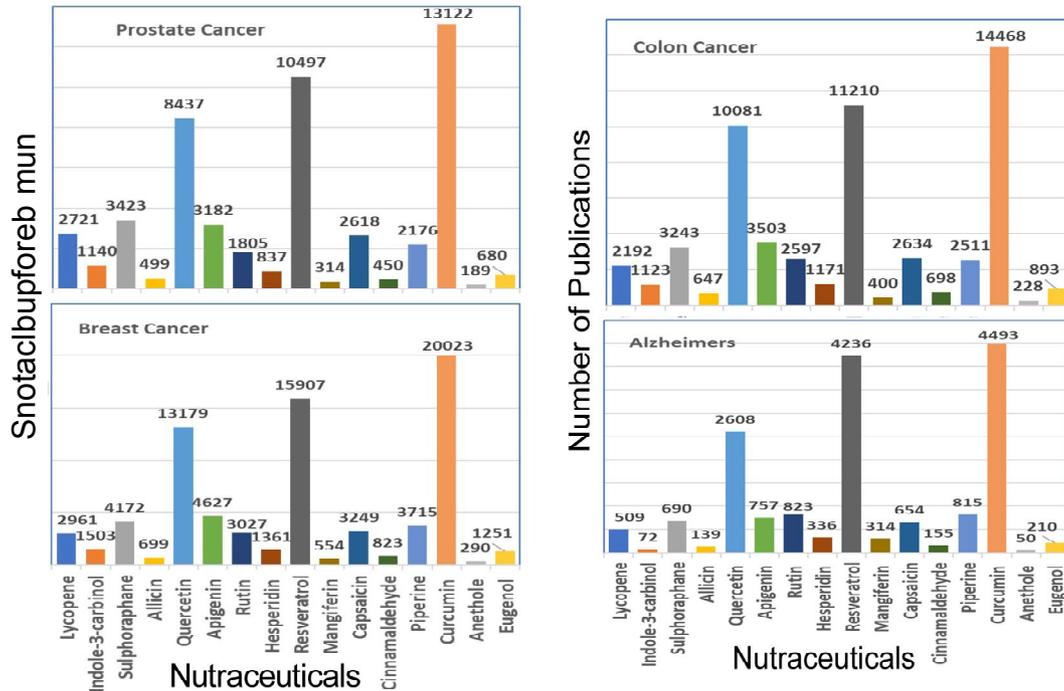


Fig. 2. Number of publications pertaining to the nutraceutical phytochemicals of selected fruits, vegetables, and spices capable of preventing or containing diseases such as prostate, breast and colon cancer and Alzheimer’s disease through their ability to inhibit activation of TNF (tumor necrosis factor) and NF-kB (nuclear transcription factor). *Source:* National Center for Biotechnology Information, USA.

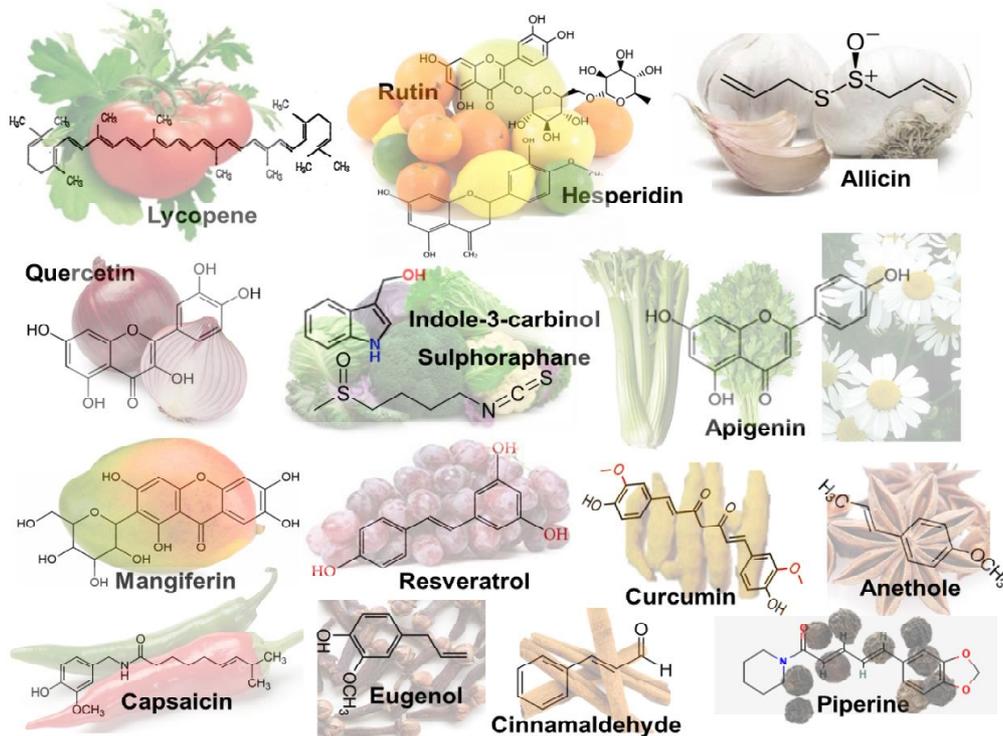


Fig. 3. Nutraceutical components of selected fruits, vegetables, and spices capable of inhibiting nuclear transcription factor and tumor necrosis factor (NF-kB/TNF). The activation of TNF/NF-kB has negative effects on cellular function.

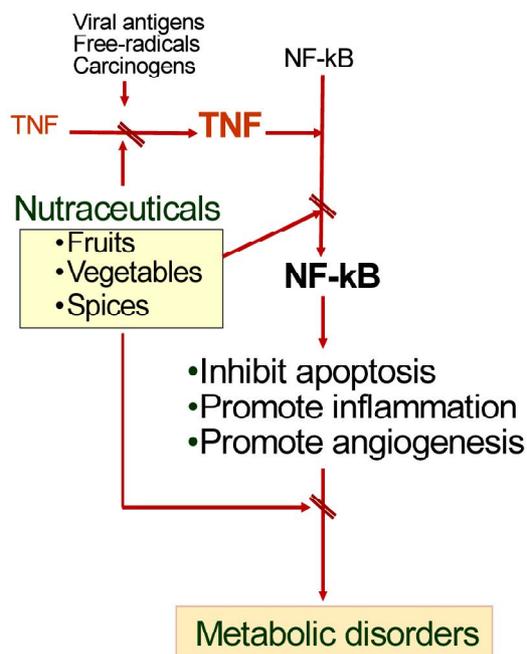


Fig. 4. Simplified schematic presenting the mechanism of activation of tumor necrosis factor (TNF) and nuclear transcription factor (NF- $\kappa$ B). Nutraceuticals derived from fruits, vegetables and spices play a role in the inhibition of NF- $\kappa$ B and suppress cellular processes (inflammation, angiogenesis, and apoptosis) that lead to metabolic disorders (Bold faced TNF and NF- $\kappa$ B represent active forms).

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