

ANTI-INFLAMMATORY EFFECT OF NATURAL ORIGIN FOLK MEDICINES USED AS COMMON DIETARY SOURCES

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Abstract:

Inflammation is a natural strategy of the living body to restrain and overcome the numerous infections, and injuries any damages caused substantially by the external pathogenic invasions or other factors. Despite the beneficial aspects of acute inflammation for healing, prolonged persistence of the inflammatory response can result in redundant consequences like other diseases instigation. Therefore, the anti-inflammatory drugs implemented have the dual property of both healing and non-manifestation of undesirable pain, soreness and edema. Non-steroidal drugs are one of the most substantial and effective anti-inflammatory drugs but their use is limited due to their side effects inclusive of gastrointestinal tract damage and renal destruction. Substitution of these chemical and synthetic drugs is effectively accomplished by herbal and natural anti-inflammatory products. Naturally occurring products like citrus fruits, curcumin, white willow bark and green tea along with their corresponding anti-inflammatory properties are discussed. Apart from herbal sources, animal-derived products like fish oil also serve as a rich source of polyunsaturated fatty acids which extensively assists in the anti-inflammation.

Keywords

Inflammation; anti-inflammatory drugs; polymethoxyflavones; flavonoids; cytokines

1. INTRODUCTION

Perpetual exposure of a living body to the environment can lead to numerous consequences out of which infections, injuries, wounds, lesions and other damages caused to the body comes under the negative impacts (Ferreira et al., 2006). To overcome these destructions and damages caused by the exposure to harmful environment inclusive of several pathogenic microorganisms, the body has its own way of protecting itself as a defence mechanism (Vyas K et al., 2014). Inflammation is such a strategy of securing the body as a response to all the wounds and injuries which is characterised by some sort of anomalous functioning of the body like variation in the flow rate of blood, elevation of the blood vessels in its permeability and movement of leukocytes towards the injured and infected areas (Reinke JM et al., 2012, Medzhitov R et al., 2008, Serhan CN et al., 2010). It is an immune response to heal the body which is initially triggered by any infections and injuries caused (Zeyda M et al., 2009). Inflammation can be categorised as acute or chronic based on their duration of persistence (Higgs GA et al., 1983). Although they are sorted as beneficial for the body to heal, occasional drawbacks include pain, soreness, swelling and transient discomfort. Chronic inflammation is far more obstructive as the prolonged acute inflammatory responses can eventually result in a multitude of other diseases like diabetes, cancer, arthritis by the destruction of tissues, internal bleeding over the passage of time (Baecklund E et al., 2006, Federico A et al., 2007, Del Campo JA et al., 2018). Accordingly, there is a rational necessity for some anti-inflammatory approaches to overcome these limitations as well as accomplish the healing processes.

2. INFLAMMATORY PATHWAYS

Pathways of the inflammatory activities are stimulated by wounds and tissue injuries leading to the exhibiting of activator hormones like prostaglandins and thromboxanes elevating the inflammatory response (Higgs GA et al., 1983, Kuehl FA et al., 1980, Smith HS et al., 2006). Arachidonic acid pathway is considerably one of the most studied inflammatory pathways specified by the release of this particular acid over the injured and infected tissues or cellular components (Vane JR et al., 1976). Subsequently, activities of the cyclo-oxygenase enzymes convert these acids into short-lived prostaglandins and thromboxanes hormones which are responsible for the inflammatory cascade events (Ricciotti E et al., 2011, Tak PP et al., 2001). Another notable pathway is the nF-kb inflammatory cascade which commences with the detection of any infectious agents, damaged tissues or free radicals and consequently directing the nucleic acids to generate inflammatory cytokines as an immune response (Afonina IS et al., 2017). Non-Steroidal Anti-inflammatory Drugs (NSAIDs) such as ibuprofen, methocarbamol, ketoprofen, indomethacin is of prime importance in their major role of restricting the enzymatic cyclo-oxygenase (COX) pathway and subsequently curtailing the release of inflammatory prostaglandins and thromboxanes to reduce the inflammatory response (Harris RE et al., 2005, Suleyman H et al., 2007, Díaz-González F et al., 2015, Ahmed T et al., 2019).

3. MODE OF ACTION OF ANTI-INFLAMMATORY DRUGS

During injury, damaged cells activate arachidonic acid pathway and several other enzymatic pathways for the production of prostaglandins, thromboxanes, and leukotrienes, resulting in pain, edema due to inflammation taking place. As a result of injury, NF-kB (nuclear factor-kB) inflammatory protein activates by the I κ -kB (I κ B kinase) enzyme and enters into the cell nucleus to activates the transcriptional machinery (Fischer C et al., 2019). It acts as transcription factor for the expression of gene and production of cytokines, chemokines, and adhesion molecules to enhance the inflammatory response (Talalay P et al., 2003, Mills EL et al., 2018). The releases of the pro-inflammatory cytokines (Interleukins (IL) and tumor necrosis factor (TNF- α)) are necessary for the activation of neutrophils and phagocytosis, migration of endothelial cell and synthesis of inflammatory lipid prostaglandin E2 (PGE2) (Wajant H et al., 2003).

Anti-inflammatory drug such as NSAID interact with the pro-inflammatory cytokines and the inflammatory cascade pathway (Vane J et al., 1987). They prevent the prostaglandin biosynthesis pathway by blocking the COX pathway to prevent the formation of other inflammatory mediators (Smith CE et al., 2017). Other than NSAID different natural products inhibits the NF-kB inflammatory pathways (Frantz B et al., 1994, Yuan G et al., 2006).

However, the key limiting factor for the use of these drugs is their consequential side effects on other parts of the body (Brune K et al., 2015). Several studies conducted have distinctively manifested that they have adverse effects on the gastrointestinal pathway, gastritis, chronic renal and kidney failure, ulcer formation and impediment of tendons, cartilage and ligament healing and muscle regeneration (Maroon JC et al., 2010, Sostres C et al., 2010, Fischbach W et al., 2019). These side effects can be justified by the relative inhibition of COX-1 pathway which is mainly responsible for securing the gastric mucosa (Greenhough A et al., 2009, Wongrakpanich S et al., 2018, Babladi VP et al., 2019). Therefore the only alternative for the replacement of these chemically contrived drugs is the naturally occurring products like herbal and organic sources such as phytochemical compounds with high anti-inflammatory activities (Trieu V et al., 2019).

4. NAUTRAL ANTI-INFLAMMATORY COMPOUNDS

Nature provides us several products having anti-inflammatory and pain-relief property (Debnath T et al., 2013, Geronikaki AA et al., 2006, Rius B et al., 2016, Lesjak M et al., 2018). Normal dietary products and food items used in our daily life have potential anti-inflammatory activity therefore; they are used as folk or traditional medicine or therapeutic agent for pain-relief. Several food or dietary products containing phytochemicals: *phenolic, polyphenolic, terpenoids, flavonoids and sulphur-containing compounds* are potentially used as pain-relieving drug molecules (Yoon JH et al.,

2005, Serafini M et al., 2010, Oliviero F et al., 2018) These products such as esculetin, fraxetin, daphnetin, coumarin have heterocyclic moiety, similar to the flavonoids controls the cell death, synthesis free radical, edema and inflammation of wound site (Di Carlo G et al., 1999, Oyagbemi AA et al., 2009, Marzocchella L et al., 2011) These molecules inhibits the prostaglandin synthesis pathways, activity of lipoxygenase and cyclooxygenase enzyme and nF-kb inflammatory cascade (Stogniew M et al., 2002). Some of these natural anti-inflammatory products are briefly discussed:

Citrus peel

Inclusive of herbal products, citrus fruits like oranges which belong to the Rutaceae family dispense multitude of important dietary nutrients and other beneficial nutraceutical sources (Gosslau A et al., 2014). Anti-inflammatory activity is one of its key aspects accomplished by the bioactive compounds like polyphenolic flavonoids (Khan RA et al., 2016). Apart from manifesting anti-inflammatory properties, these bioactive phytochemicals also exhibit a wide range of other physiological features like anti-microbial, anticancer and anti-atherosclerosis activities (Bodîrlău R et al., 2009, Ho CT et al., 2012, Parhiz H et al., 2015). Polymethoxyflavones (PMFs) are one of the polyphenolic compounds found in the peels of citrus fruits like oranges which are of paramount importance in inflammatory cascade events suppression (Chen XM et al., 2017). Other than PMFs, its hydroxylated derivatives, nobiletin, tangeretin and terpenoids are also responsible for the inhibition of COX and nF-kb activity pathway consequently assisting the anti-inflammation process (Joe B et al., 2004, Gao Z et al., 2018).

Curcumin

Out of the three vital components of turmeric specifically curcumin, demethoxycurcumin, and bis-demethoxycurcumin, the constituent responsible for rendering the maximal anti-inflammatory activity is curcumin (Menon VP et al., 2007, de Almeida M et al., 2018). Curcumin or diferuloylmethane is the fundamental yellow pigment belonging to the Zingiberaceae family which accounts for the imparting of yellow color in turmeric (*Curcuma longa*). Anti-inflammatory action of curcumin is attributed to its substantial pleiotropic property facilitating the association with the target molecules implicated in the inflammation process (Jurenka JS et al., 2009, Abdollahi E et al., 2018). The strategy with which curcumin endeavours the anti-inflammation is by curtailing the enzymatic action of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS) and lipoxygenase (Rao CV et al., 2007). Generation of inflammatory cytokines inclusive of interleukin-12 (IL-12), tumor necrosis factor- α (TNF- α) and monocyte chemo-attractant protein -1 (MCP-1) is strenuously impeded which subsequently exhibits the anti-inflammation (Chainani-Wu N et al., 2003, Cheng AC et al., 2018). Activities of other components involved in inflammation which are predominantly obstructed by curcumin include leukotrienes, interferon-inducible proteins, hyaluronidase, thromboxanes, collagenase and elastase (Mahdi JG et al., 2010).

White willow bark

White willow bark has been employed since time immemorial as an herbal medication for the anti-inflammatory, anti-pyretic and analgesics activity. Salicin is predominantly considered as the key constituent for the manifestation of the anti-inflammatory property along with relative salicylates, flavonoids and other polyphenols (Shara M et al., 2015, Setty AR et al., 2005). Anti-inflammation is achieved through the down-regulation of cyclo-oxygenase pathway and NF-kB with the suppression of TNF- α which is an approach equivalent to that of non-steroidal anti-inflammatory drugs particularly aspirin (Maroon JC et al., 2006, Graf J et al., 2000, Bonaterra GA et al., 2010). Side effects like epigastric disturbances, nausea and heartburn led to the preferential utilization of this natural product as opposed to the chemically synthesized aspirin (Cabrera C et al., 2006).

Green tea

Green tea is predominantly attributed to its potential to avert cardiovascular and oncogenic activities in addition to its anti-inflammatory properties (Graham HN et al., 1992). The chief component of green tea responsible for manifestation as an anti-inflammatory agent is the poly-phenol epigallocatechin-3 gallate which is one of the most substantial catechin found in green tea (Tipoe GL et al., 2007, Afzal M et al., 2015). Its mechanism of anti-inflammatory action is characterized by the inhibition of transcription factor NF-kB and obstructing the interleukin-1b production. Its

complementary assistance in the suppression of aggrecanases also prevents cartilage degradation (Chu C et al., 2017). The chief preventive activity of green tea leading to its concession as an anti-inflammatory agent is the restriction of inducible nitric oxide synthase (iNOS) pathway resulting in impeding of peroxidation with nitric oxide radicals and oxidative stress (Ohishi T et al., 2016). Tissue wounds and lesions like hepato-cellular necrosis instigated by carbon tetrachloride are also efficiently recovered through the anti-inflammation of green tea (Chow HS et al., 2003, Cyboran S et al., 2016). Minimal side effects include abdominal discomfort corresponding to its caffeine content (Harris WS et al., 2004).

Fish Oil

The considerable effect of fish oil in its rendering of anti-inflammatory activity can be immensely exhibited for the treatment of numerous inflammation caused ailments (Wall R et al., 2010, Ellulu MS et al., 2015, Zadeh-Ardabili PM et al., 2019). Enriched with omega-3 polyunsaturated acid, the main constituents of fish oil responsible for exhibiting the anti-inflammatory activity are eicopentanoic acid (EPA) and docosahexanoic acid (DHA) which impedes the arachidonic acid pathway of anti-inflammation (Rubio-Rodríguez N et al., 2012, Amin M et al., 2018, Innes JK et al., 2018). Fish oil can be procured either through enzymatic extraction or methods of green extraction such as exploitation of CO₂ for supercritical fluid extraction (SFC-CO₂), microwave assisted extraction (MAE) and ultrasound assisted extraction (UAE) (Ramakrishnan VV et al., 2013, Sidhu KS et al., 2003). These methods of extraction are favoured over the traditional and conventional methods due to their preferential advantage specifically the optimisation of yield and productivity, lesser time consumption and minimising the temperature for operation (Sidhu KS et al., 2003). Implementation of fish oil has been limited due to the foul odour and brisk rancidity of the polyunsaturated fatty acids when they come in contact with air and moisture (Lee KY et al., 2012).

5. CONCLUSION

Considering the chemical drugs for anti-inflammatory activities, NSAIDs are one of the most substantial and effective drugs with favourable outcomes. Since implementation of NSAIDs have been shown to manifest numerous side effects specially targeting the gastro-intestinal tract, seeking of substitute natural anti-inflammatory drugs such as herbal, animal-derived, organic and dietary supplements has been substantiated to be a better choice. The basic essence of blocking characteristics between the NSAIDs and natural drugs remains the same as in the COX inflammatory activity inhibition as well as nuclear factor pathway obstruction.

Several research studies conducted have shown that the key feature attributing to the underlying mechanism of natural drugs anti-inflammatory activity is the inhibition of NF-kb activation along with other inflammatory cascade mediators. Polyphenolic compounds like polymethoxyflavones in the citrus fruits peels such as oranges, curcuminoid compound like diferuloylmethane (curcumin) in turmeric, salicin in bark of white willow, catechin compound like polyphenol epigallactocatechin-3 gallate in green tea, pomega-3 polyunsaturated fatty acid such as eicopentanoic acid (EPA) and docosahexanoic acid (DHA) in animal derived product like fish oil are some of the naturally acquired products which exhibits great anti-inflammatory properties so as to favour its preferential implementation over chemically synthesized drug without any side effects.

Considering the advanced researches and technology to assist the efficient and precise therapeutic effect of these natural anti-inflammatory products, encapsulation serves as a delivery technology (Jung J et al., 2013). This type of drug delivery system is a good candidate for susceptible substances and their entrapment.

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