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Therapeutic potential of pomegranate antioxidant compounds in ameliorating opiate addiction

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Abstract
Opioids are ethical drugs yet one of the most abused on a global scale. They are used as analgesics in the management of moderate to severe pain especially those associated with chronic and terminal diseases. Although this class of drug presents fewer side effects, the most worrisome are tolerance, dependence and addiction. The pharmacological management strategies of opiate addiction require oral administration of long-acting opioid receptor agonists or partial agonists and opioid antagonists. However, these measures present marked demerits that include withdrawal symptoms, dependence, relapse of opiate abuse and in some instances unfavourable pharmacokinetic profile of the drugs. Pomegranate fruits are enriched with antioxidant polyphenols that modulate addiction pathways and neurotransmitters. These polyphenols have the tendency to antagonize or block opioid-induced tolerance and withdrawal symptoms. This review article highlights the potential of pomegranate antioxidant-rich compounds in ameliorating opiate addiction. Furthermore, studies that show potential for synergism between the conventional opioid agonists and antagonists in the pharmacotherapy of opiate addiction are also explored.

Keywords: Opioids, addiction, pomegranate, polyphenols

Introduction
Opioid compounds are primarily administered to patients for the management of moderate to chronic pain. They work in the body by mimicking the action of endogenous opioid peptide [1]. However, unlike the endogenous peptides, opioid compounds lower the threshold for reward system thereby making the body adjust through some compensatory mechanisms [2]. The hallmark of systemic homeostatic process to opioid ingestion is addiction, manifested as drug craving and compulsive drug seeking. Lack of fulfilling this craving leads to homeostatic imbalance in the form of withdrawal syndromes. All opiate drugs capable of producing analgesia also produce euphoria which is the initiating factor for the development of tolerance, dependence and addiction [3].

The abuse of opioids alters brain structure and function that persists long after drug use has ceased [2]. Therefore, there is high risk of relapse even after long term abstinence with devastating consequences. Thus, opiate addiction is a multifocal condition that requires a pedagogic and comprehensive strategy to manage. It is also influenced by the complex interplay of environment and genetics; epigenetics. Other components of drug addiction are biological, social and psychological factors. The presence of biological component makes it difficult to achieve and maintain abstinence without treatment. Ultimately, a comprehensive multifaceted approach to therapy is required to attain a sustained abstinence from drug abuse [4].

Pharmacological management of opiate addiction requires substitution of short acting μ opioid receptor (MOR) agonists such as heroin with oral administration of long acting agonists (Methadone and Levomethadyl acetate) or partial agonists (buprenorphine) which do not have tendency for addiction [5, 6]. However, these long acting substitutes are also associated with withdrawal symptoms which are even more long lasting and more debilitating than those caused by morphine and heroin. Withdrawal symptoms are the chief causative factor of dependence and relapse of opiate abuse. Opioid antagonist (e.g. naloxone and naltrexone) are also used in addiction management. The lack of oral administration, short half-life and high rate of withdrawal syndromes makes naloxone unsuitable in addiction management. Newer approaches to therapy involve the use of non-opioid compounds such as clonidine, flurazepam and diphenoxylate for detoxification to block withdrawal syndromes [7].

A nutrigenomic study has shown that fruits containing polyphenol compounds, are capable of inducing a feeling of well-being after ingestion. And this pleasurable sensation was attributed to the ability of polyphenols to modulate central reward pathways [8]. Antioxidant rich compounds which target various addiction pathways and neurotransmitters have recently been considered in blocking opioid induced tolerance and withdrawal symptoms [9, 10]. Ellagic acid, a pomegranate antioxidant compound has also been shown to alleviate morphine dependence and tolerance by blocking calcium channels [11].

This article reviews available literature on the potential of pomegranate antioxidant compounds to be used in the amelioration of opiate addiction. In addition, the article also exploits studies that have shown potential for synergism with available conventional opiate agonists and antagonists used in the pharmacotherapy of opiate addiction.

Addiction to Opioids

Opioids are one of the most abused drugs globally [12]. They are also referred to as narcotics and classified as ethical drugs that require prescription before they are dispensed to patients. This class of drugs have a long history of application in analgesia. They have lower tendency to cause gastric bleeding, nephrotoxicity and hepatotoxicity compared to the Non-Steroidal Anti-inflammatory Drugs (NSAIDs) and other drugs used in pain management. Additionally, they are more suitable for moderate to severe pain especially those associated with chronic diseases such as cancer and other terminal diseases. Although there are few side effects of opioids, the most worrisome of them are tolerance, dependence and subsequently, addiction. Tolerance also increases the risk of overdose which may result to fatal consequences [13].

Some opiate addiction problems are as a result of long term use of opioid analgesics for pain management. Significant morphological and functional changes have been found in patients abusing prescription opioids and illicit opioids, leading to intense and/or uncontrollable drug craving, compulsive drug seeking and use that persist in the face of devastating consequences [14].

The development of addiction usually begins with the liking of the substance in question, followed by derivation of pleasure from taking such substance [15]. Regular consumption of the drug leads to tolerance, a state whereby the normal dose that gives pleasure no longer does so thereby necessitating the need for high dose intake. The major neurotransmitter in reward system is dopamine. Dopamine supersensitivity can enhance the incentive motivational properties of reward cues, and reward cues contribute to the maintenance and severity of drug addiction [16].

In opiate addiction, continuous administration of opioid compound results to reduced sensitivity of MOR on neurones located in locus cereleus (LC) to opiate compounds and a consequent reduction in the amount of noradrenaline (NA) released [2]. Lack of or low amount of NA causes drowsiness, low blood pressure and low respiratory rate associated with opiate abuse. The absence of opiates on the other hand leads to wakefulness, fast respiratory rate, increased blood pressure, and general alertness, among other functions making the individual uncomfortable and an urgent need to seek the substance of abuse. This state is called drug dependence where the victim needs to keep taking the drug to avoid a withdrawal syndrome. While a person initially chooses to take drugs, over time the effects of prolonged exposure on brain functioning compromise that ability to choose, and seeking and consuming the drug become compulsive, often eluding a person's self-control or willpower [17].

Apart from the problem of compulsive drug seeking behaviour, patients are also at risk of developing other mental and physical illnesses related to a drug-abusing lifestyle or the toxic effects of the drugs themselves. Additionally, the dysfunctional behaviours that result from drug abuse can interfere with a person's normal functioning in the family, the workplace, and the broader community. Due to the numerous dimensions associated with drug abuse and addiction and the consequential disruption of several aspects of a person's life, treatment approach is generally complex [18].

Oxidative Stress in Opioid Addiction

Opioids consumption have been associated with increased levels of oxidative stress biomarkers such peroxide malondialdehyde and reduction of vitamin E [19]. Fatty acids in the body are oxidised by reactive oxygen species in the body thereby increasing malonaldehyde levels. This unfavourable oxidative state caused by an increased free radicals levels and a compromise of endogenous antioxidant system is thought to play a major role in morphine induced withdrawal syndromes during abstinence [20].

Heroin addiction is also associated with reduction in the activities of superoxide dismutase (SOD) and glutathione peroxidase. There is also a decrease in the level of some essential metals such as iron, manganese, magnesium, and titanium and an increase in aluminium, copper and calcium levels [21]. Co-administration of morphine and alpha lipoic acid also increases glutathione and glutathione peroxidase but lowers malonaldehyde, nitrous oxide (NO) and glutamate activities. Morphine induced tolerance also increases the expression of mRNA proteins for inducible NO but not neuronal NO [22].

However, supplementation with vitamin E plus selenium or exogenous melatonin minimised the destruction of bio-elemental and antioxidant enzymes activities [16]. Another study also showed that co-administration of morphine with alpha lipoic acid minimised lipid peroxidation and improved tocopherol level in the body [23].

Oxidative stress induced by opioid addiction may result from either direct or indirect effect of the abused drug. It could also occur either after exposure to drug or during withdrawal from drug use [24].

Pharmacological intervention in opiate addiction

Addiction has been psychoanalytically interpreted as a pleasure seeking pathology [25]. Because addiction is a chronic disease, it requires long time or episodic intervention to achieve the ultimate goal of sustained abstinence and recovery of victims lives. Treatment usually depends on the substance of abuse and patient characteristics. Most patients abuse more than one drug and thus, require more than one treatment approach.

Behavioural therapy is an important factor to be considered in addiction intervention. Medications are also necessary to make patients more receptive to behavioural therapy. Genetic factors have also been reported to play a part in variation to medication use [26, 27].

As earlier mentioned, drug addiction causes structural and functional changes in some brain circuits including those involved in reward and motivation, learning and memory, and

inhibitory control over behaviour. That is why addiction is referred to as chronic disease of the brain. Some individuals are more vulnerable than others to becoming addicted, depending on the interplay between genetic makeup, age of exposure to drugs and other environmental influences [28]. Initial consumption of opiate drugs in the absence of pain and a consequent derivation of pleasure creates a conditioned association. An attempt to quit opiate intake leads to withdrawal syndromes which have been linked to calcium and potassium ion channels activities. Addictive opiate compounds bind to MOR which subsequently causes dopamine release. The binding of dopamine to neurones of the reward system elicits pleasurable sensation usually derived from activities like sex and food intake [29]. Dopamine also causes calcium ion channel stimulation and potassium ion channel inhibition. Long acting opiate agonists used in addiction management act on MOR receptors without causing dopamine release. Furthermore, they have an opposing activity on calcium and potassium ion channels. Blockade of voltage-gated calcium channels and excitation of potassium ion channels causes hyperpolarisation and inhibition of adenylyl cyclase activity. Thus, calcium channel blockers such as fenodipine and verapamil are useful in the treatment of withdrawal symptoms [9].

Centrally acting noradrenergic antagonists such as clonidine are also used in addiction pharmacotherapy. They block the adrenergic effects associated with addiction highlighted earlier by inhibiting both central and peripheral release of NA [30, 31].

It should be understood that the abnormalities that result to dependence can easily be reversed by detoxification within days or weeks after halting opioid use. On the contrary, abnormalities leading to addiction are more wide-ranging and complex that require longer time to return to normal [32].

Role of pomegranate in managing opioid addiction

Pomegranate fruit is enriched with antioxidant polyphenols that have attracted the attention of the scientific community in recent decades [33]. Several studies on pomegranate involves whole fruit crude extracts, pharmaceutically formulated extracts, whole fruit commercial juice, aril extracted juice and isolated compounds from the peel and arils. The most abundant polyphenol in the fruit is punicalagin, an ellagic acid oligomer [34].

The central activity of punicalagin and ellagic acid have been demonstrated by various studies especially in the prevention of neurodegenerative diseases including aging [35, 36]. An *in vivo* study using the rat formalin assay has shown that the antinociceptive effect of ellagic acid was via binding to both central and peripheral opioid receptors in a dose dependent manner [37]. Furthermore, co-administration of ellagic acid with naloxone, a non-selective opioid antagonist alleviated both peripheral and central antinociceptive effects [37]. In a related study using acetic acid induced abdominal writhing test, pre-treatment of animals with L-arginine, a nitric oxide precursor, and methylene blue, a guanylate cyclase inhibitor, both enhance the antinociceptive effects of ellagic acid. On the contrary, glibenclamide, an ATP-sensitive K^+ channel blocker, significantly reversed antinociceptive activity induced by ellagic acid. These studies corroborate the central and peripheral activities of ellagic via opioidergic pathway and L-arginine-NO-cGMP-ATP sensitive K^+ channels pathway [38]. Similarly, Ghorbanzadeh *et al.* (2014) also showed the involvement of the l-arginine/NO/cGMP/KATP channels pathway in ellagic acid-induced antinociception [39]. In another study, ellagic acid blocked the development of morphine induced tolerance to analgesia and dependence. It also prevented naloxone precipitated withdrawal syndrome [9]. In an *in vitro* studies using rat uterus, the spasmolytic effect of pomegranate hydroalcoholic extracts was shown to involve calcium channels [40].

Pomegranate fruit extract has been shown to possess gene stabilising effect in carcinogenesis [41]. This function could also be applicable in addiction prevention where individuals who are genetically predisposed can benefit from the co-administration of pomegranate and opioids. Alternatively, a low dose pomegranate concomitantly administered with low dose morphine may produce a synergistic effect thereby preventing the development of tolerance as a result of high dose of opioids. Pomegranate polyphenols have also been demonstrated to be effective in managing oxidative stress and its related diseases [42]. Antioxidant polyphenols have also been shown to improve cognitive performance [43, 44]. This would benefit the reduced mental function associated with addiction.

Conclusion

The findings of this review suggest that pomegranate polyphenols have activity against the major components of addiction; tolerance, dependence and withdrawal syndromes. Studies have also shown their potential use in the alleviation of oxidative stress and reduced cognitive function associated with opiate addiction. They can serve as adjuvants to opioid analgesics in the management of pain to attenuate dependence**.** They can also be used as adjuvants in opiate addiction therapy to alleviate withdrawal symptoms after detoxification.

Conflict of Interest

The authors declare no conflict of interest.

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