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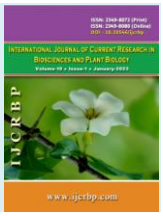

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Tobacco - The Antithesis

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Abstract

Tobacco in any form is harmful. It affects our heart, lungs, blood circulation, stomach, mouth, eye, skin, reproduction, and fertility, but nicotine which is the main constituent of tobacco has a history, which is irreprehensible. Even after it was popularized in Europe tobacco was considered a panacea for more than 65 ailments. These include treatment of minor problems like bleeding, fever, and insect bite to major pathologies like rodent ulcers, strangulated hernia, tetanus, gout, and neuralgia. Recent epidemiologic and animal model studies have proven various potential benefits of tobacco in diseases like Parkinsonism, Alzheimer's disease, autoimmune conditions, inflammatory diseases, and endometrial and thyroid carcinoma. If we can get to the bottom of the cellular and molecular mechanism of the components of tobacco and repress the detrimental effect of tobacco with more experiments and research, tobacco can be the panpharmacon. This topic incorporates the history, beneficial effects of tobacco, and the mechanism of action of its components so that it may be used for the benefit of society.

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Introduction

The tobacco plant 'nicotiana is the most notorious herb ever in history. According to WHO it kills more than 8 million people each year[1]. Tobacco in any form is harmful. It affects our heart, lungs, blood circulation, stomach, mouth, eye, skin, reproduction, and fertility[2], but nicotine which is the main constituent of tobacco has a history that is irreprehensible[3,4,5]. The word nicotine itself has a history. It was named in honour of

Jean Nicot, French ambassador to Lisbon, Portugal who in 1559 sent samples of the herb as a medicine to the court of King Francis II, and queen mother Catherine de Medici after he witnessed the successful recovery of a case of Noli me-tangere (an old term used for slow spreading ulcerating lesions of skin most probably basal cell cancer or rodent ulcer) on the cheek of one of his pages which had already spread to the cartilage of nose. He had also found it successful in the treatment of 2-year-old ulceration of the leg, severe ringworm infection of the face, a case of scrofula, and many more[3].

Even after it was popularized in Europe about the deleterious health consequence of chronic tobacco smoking and chewing[6,7], tobacco was considered a panacea for more than 65 ailments. Recent epidemiologic studies and animal models have proven various potential benefits of tobacco in diseases like parkinsonism[8,9,10], Alzheimer's disease[13], autoimmune conditions, inflammatory diseases[14,15,16,], and endometrial and thyroid carcinoma[22,23]. Thorough knowledge of tobacco's history is relevant to the current problem of differentiating socially or medically-approved use from substance abuse and addiction.

Origin and history

Nicotiana belongs to the family Solanaceae which consists of more than 60 species. *Nicotiana tabacum*, commercially used for tobacco production originated from South America, and *Nicotiana rustica* from North America[3]. The indigenous people in the Peruvian Amazon region consider tobacco as the father of all plants and for them, healer means "he who eats tobacco"[5].

It was Columbus who had noted in 1492 about two native Indians carrying dried leaves in a canoe brought the knowledge of Tobacco to Europe. In 1500, Portuguese explorer Pedro reported tobacco use in treating many ailments. A Spanish priest Bernado de Sahagun in 1529 had mentioned the use of tobacco in persistent headaches[3].

Even though Franciscan monk Andre Thevet (1555) and physician Conrad Gesner raised concerns about the toxic property of this plant, tobacco gained wide popularity in Europe during the 16th century and various monographs published during that period are evidence of this[3]. Nicholas Monardes in his famous book (1565) mentions the use of tobacco for the treatment of 65 ailments[4].

In 1567 Liebault and Estienne published a book "Maison Rustique" 1567 in which there was a chapter entitled "Nicotiane" which describes various virtues of the nicotine plant. However, this initial flash of ardor and fervor for the medicinal use of tobacco was being questioned by others for its efficacy[4].

In 1602 Philarates raised criticism against the indiscriminate use of this herb in all age groups without a specific dosage. This was reiterated by Vaughan and John in 1612[3] and in 1633 James Hart, another Doctor, wrote 'let no man deceive himself so farre, as to think this to be some famous Panacea, Nepenthe or some golden Elixir, whereof hath beene much bragging, but small benefit as yet reaped', and added 'And of this, I am verily persuaded, that the excessive and disorderly use of this simple, is as no small cause, as of the more frequent reigning of divers dangerous diseases among us[6]. Then as the 17th century progressed, Doctors increasingly mistrusted tobacco as medicine but this did not prevent its position in pharmacopeias. John Wesley in 1747 recommended tobacco for earache and piles. Such advice continued as late as the edition of his book in 1847[7].

In the 19th century efforts to isolate nicotine found success (1928). Nicotine began to be used alone in measured doses. But the knowledge that the plant contains a dangerous alkaloid made the medical world more distrustful. Even then during this century tobacco was used successfully in various diseases with different routes of administration (Stewart 1964)[3].

Tobacco smoking was adopted more for pleasure than its medicinal uses in western and American colonies. Even then the therapeutic uses didn't taper in the 20th century. In 1926, Moll successfully treated 13 patients with post-encephalitic parkinsonism with subcutaneous nicotine injection. He stated that 'although the benefit was only temporary the immediate results were indisputable'.[8]

The practice of chewing tobacco also goes back hundreds of years. Before the coming of Columbus to America, the native Americans had a common practice of chewing tobacco. Eventually, cigarettes have outgrown and replaced tobacco chewing as the dominant form of tobacco consumption. But tobacco

chewing is now also followed in African and South Asian countries.[9]

Newer medical applications for tobacco

The evolution of information and technology along with the changes in the socio-economic-political climate has led to the transformation of the opinion of the medical community about the use of tobacco. For even though man biologically has remained the same, medicine and medical knowledge have changed and many concepts prevalent before the 19th century are no longer valid or usable. Thus, various types of research are being conducted to study the efficacy and safety of nicotine in various diseases.

Parkinsonism is a neurodegenerative disorder of the motor system affecting 6.2 million people worldwide. A study by Yuan Cheng et al (2020)[10] shows that death from Parkinson's disease was found to be 34.7% lower in smokers than nonsmokers and smokers were found to have a 30-40% lower risk of Parkinson's disease. Ahmad Alhowail et al (2020) in his review describe the pathogenesis of Parkinson's disease involving the loss or degeneration of dopaminergic neurons in the substantia nigra of the midbrain and the protection provided by nicotine through the P13K/Akt pathway. He also mentions that nicotine through inhibition of Sirtuin 6 (SIRT 6), an NAD+ dependent class III deacetylase reduces apoptosis and increases neuron survival.[11]Also, studies[12] show that in patients taking L-DOPA, nicotine reduces L-DOPA induced involuntary movements which is a serious side effect of the therapy. Yash Sharma et al (2018) in his study successfully used tobacco mosaic virus coat to block the LRRK-2 (leucine-rich repeat kinase -2) receptor, the mutations of which are the most common cause of autosomal dominant Parkinson's disease[13].

Nicotine also protects from cognitive decline and behavioral changes in Alzheimer's disease. The pathogenic mechanism of the decline of acetylcholine synthesis and loss of cholinergic neurons of the basal forebrain that project to the cortex and hippocampus is overcome by nicotine through the cholinergic actions on nAChRs (nicotine acetylcholine receptors)[13]. Nicotine patches are being tried for this[4,11].

In the case of hypothyroidism Alhowail et al (2021) mentions that out of the thyroid receptors α and β, thyroid β receptors are present in the brain abundantly in the hippocampus which is the part of the brain involved in memory formation and nicotine administration activate thyroid β receptors thereby enhancing learning and memory. Along with this, memory impairment caused by hypothyroidism was found to be improved by nicotine through the modulation of calcineurin. Calcineurin regulates calmodulin-dependent protein kinase II which improves synaptic plasticity[11].

David et al (2006) in their review mentions the exploitation of nicotinic anti-inflammatory pathway for the treatment of inflammatory diseases. It is an endogenous anti-inflammatory mechanism to limit the self-damage caused by excessive inflammation which is normally controlled by CNS through the production of adrenocorticotropic hormone, glucocorticoids, substance P, and melanocyte-stimulating hormone[15].

Activation of inflammatory cells mainly monocytes and macrophages through; for example, bacterial lipopolysaccharide action on toll-like receptors activates the nuclear factor- κB and results in the production and release of various proinflammatory cytokines. These proinflammatory cytokines can be inactivated by the α7 nAChR-dependent cholinergic anti-inflammatory pathway which is triggered endogenously by acetylcholine and exogenously by nicotine. This mechanism has proven lifesaving in endotoxic shock in mice[15]. The cholinergic mechanism blocks the inflammatory cytokine production by preventing the inhibitory κB protein from degradation thereby preventing activation of NF-κB (this mechanism also functions in other cells like endothelial cells, microglia cells, etc.) or nicotine acts by suppressing pro-inflammatory cytokine release by activation of STAT3 and SOC3 signaling cascade. This mechanism can be utilized in cases of skin and mucosal pathology[15].

In Crohn's disease, a study[18] conducted on 10 patients with nicotine enemas showed clinical as well as pathologic improvement. Animal model studies[19,20] show the effect of nicotine also depends on the location of the inflammation. A protective effect was seen in the case of the colon but not in the small intestine.

In Ulcerative Colitis Studies show that current smokers have a lower risk of developing ulcerative colitis compared to ex-smokers and nonsmokers. The main mechanism is proposed to decrease the production of proinflammatory cytokines and promote the α7nicotinic

receptor-mediated anti-inflammatory effect. Also, nicotine increases ACTH and cortisol concentration which gives the benefits of steroid therapy. Clinical trials of nicotine in transdermal form were associated with improvement of symptoms[15,17].

In the case of Gingivitis and periodontitis, smoking tobacco is a major risk factor in the development and progression of periodontal disease. But according to Scott et al (2006)[15] when nicotine alone was considered a reduction in proinflammatory mediators and an increase in anti-inflammatory cytokines like IL-10and TGF-β was seen in the gingival crevicular fluid which helped to reduce the inflammatory manifestations of gingivitis and periodontitis.

Anti-inflammatory effect mainly mediated through the α7 subunit of nAChRs is the most important mechanism beneficial in Autoimmune diseases. This is found to be beneficial in conditions like Multiple Sclerosis, Rheumatoid Arthritis, Behcet's disease, Sarcoidosis, and Aphthous ulcers.

In multiple sclerosis, the subcutaneous injection was found to improve autoimmune encephalitis by reducing inflammation around the central canal and by enhancing the differentiation of undifferentiated progenitor cells to myelinating oligodendrocytes. Blockage of α9 cholinergic receptors was also involved in the protective mechanism. In rheumatoid arthritis, even though smoking is considered an environmental risk factor, nicotine when given as an injection helps to modulate TNFα response and attenuate IL-6 and IL-8 by synovicytes[17].

In Bechet's disease, many studies[21,22] show successful remission of relapsing and refractory cases of oral ulcers with nicotine patches. Genital ulcers were also treated successfully. In the case of aphthous ulcers, nicotine chewing gum was found beneficial.

A high incidence of Sarcoidosis was seen in nonsmokers compared to smokers. The nicotinic anti-inflammatory pathway protects proinflammatory mediators by macrophages thereby preventing granuloma formation[15,17].

In cancer tobacco chewing and cigarette smoking are well-established risk factors. Because of the various carcinogenic substances present in them, they cause cancer in almost all sites where they are in direct contact. But epidemiologic studies also show a protective effect in a few estrogen-related cancers where direct carcinogenesis does not play a role. They are endometrial, endometrioid, clear cell ovarian, and thyroid carcinoma[23].

In the case of endometrial cancer, all endometrial carcinomas except the rare form i.e., clear cell tumours show a lower risk in smokers, especially in postmenopausal women. Adenocarcinoma shows a reduction in risk of 35-40%[23]. Rather than the direct antiestrogenic effect, the aryl hydrocarbon receptor-mediated pathway activated by polyaromatic hydrocarbons present in cigarette smoke provides a better explanation. The activation of this pathway leads to suppression of estrogen receptor-mediated actions, induction of endometrial apoptosis, and increase in anticarcinogenic metabolites of estradiol[24],

According to various studies[25,26] in ovarian cancer, endometrioid and clear cell variants show a risk reduction of about 20% in current smokers. Baron et al (2021)[23] report that the protective mechanism of these tumours is similar to endometrial tumours.

In thyroid cancer, current smokers show a risk reduction of about 25% to 30% compared to nonsmokers. The risk reduction is slightly greater in papillary carcinoma through the medullary carcinoma also shows reduced risk. Here rather than the estrogen receptor-mediated mechanism the anti-inflammatory effect of nicotine which decreases the autoantibodies and level of thyroid stimulating hormone in smokers provides benefits[23].

Apart from estrogen-related carcinomas, if we consider epithelial neoplasms, a cohort study meta-analysis suggests that smoking increases the risk of squamous cell carcinoma and decreases the risk of basal cell carcinoma and malignant melanoma[27]. In healthy individuals, nicotine improves memory impairments caused by sleep deprivation by upregulating the mechanism of phosphorylation of calmodulin-dependent protein kinase II (CaMKII). Nicotine improves memory and learning by inducing modifications in chromatin and also by strengthening synapses[10].

Other medical applications of tobacco plant

Tobacco is an ideal plant in plant molecular pharming. This is a low-cause alternative for the large-scale

production of therapeutic agents. Antibodies derived from tobacco were found useful to combat the Ebola outbreak in Africa. The drug ZMApp is the only drug currently available for the treatment of Ebola infection. It got FDA approval in 2015. Similarly, PRX-102, a drug against Fabry's disease, and vaccines against Malaria, Anthrax, H5N1, and P2G12 an antibody against HIV have also been developed and are in various phases of trials. An immunoadhesin developed from transgenic tobacco (DPP4-Fc) showed strong adhesion with the MERS-CoV virus thereby preventing lung infection. Also, a plant adhesin NaD1 was developed from tobacco flowers which showed strong antifungal action against pathogenic fungi[4,28].

Medically beneficial components of tobacco other than nicotine

Other than the chief alkaloid Nicotine tobacco contains polysaccharides, polyphenols, and terpenoids which are also medically beneficial.

Solanesol

It is a polyisoprenoid in tobacco that possesses antioxidant, anti-inflammatory, antimicrobial, and neuroprotective actions. Through its ability to absorb ultraviolet radiation and inhibit tyrosinase enzyme, it can offer potential benefits in the treatment of pigmentation disorders. Anti-inflammatory actions by inducing haem oxygenase-1 enzyme are found to protect hepatic cells from ethanol-induced oxidative injury. Based on animal models solanesol can be used as a potent medicine for symptomatic relief in Huntington's disease. As an antimicrobial, it is effective against Escherichia coli, Pseudomonas aeruginosa, and staphylococcus aureus. Also acts as an intermediate in the synthesis of ubiquinone drugs and vitamin K2. Also beneficial in enhancing the antitumour activity of tumour suppressor drugs and reducing their toxicity[29].

Polysaccharides and polyphenols

Polysaccharides and polyphenols especially flavonoids in tobacco have tumour suppressive, immune-regulating, and antipathogenic properties[29,30]. They provide intestinal health benefits due to their prebiotic properties. Also, they act as powerful antioxidants. The reducing ability of flavonoids is comparable to ascorbic acid. The reducing property protects the cell membrane and DNA from oxidative stress thereby providing cytoprotection and delaying ageing[29,30].

Cembraniod-type diterpenes

Cembraniod-Type Diterpenes (CBD) possess antitumor, antimicrobial, and neuroprotective functions. α-CBD extracted from tobacco when treated on hepatocarcinoma cells was found to cause cell membrane alteration, decrease cell proliferation and increase apoptosis[31].

Conclusions

Social usage of tobacco in any form be it smoking or chewing or e-cigarettes can only cause adverse effects and such usage can never be justified. Tobacco smoke contains over 5000 chemicals of which more than 30 are known carcinogens[32]. An estimate shows that tobacco for a single life it saves takes away 250 deaths[33]. But if we see tobacco the plant Nicotiana from a pharmaceutical point of view, it is a herb with great potential, The various components produce diverse health benefits. If we can get to the bottom of the cellular and molecular mechanism of the components of tobacco and repress the detrimental effects with more experiments and research, tobacco can be the panpharmacon.

Conflict of interest statement

Authors declare that they have no conflict of interest.

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