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# **Understanding betel nut addiction: a review of harmful consequences, underlying neurobiology, and emerging intervention strategies**

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## Understanding Betel Nut Addiction: A Review of Harmful Consequences, Underlying Neurobiology, and Emerging Intervention Strategies

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**Abstract:** Betel nut is the fourth most commonly used psychoactive substance globally and is particularly prevalent in the Asia-Pacific region. Betel nut chewing is closely associated with a variety of health hazards, including oral cancer, cardiovascular diseases, and metabolic syndrome. This article reviews the epidemiological characteristics, health hazards, neurobiological mechanisms, and intervention strategies of betel nut addiction. The major active component in betel nut, arecoline, leads to addiction by modulating the cholinergic, dopaminergic, and glutamatergic systems, with the involvement of the gut-brain axis and immune-inflammatory responses. In terms of intervention strategies, pharmacological treatments (such as nicotinic receptor modulators), neuromodulation techniques (such as real-time functional magnetic resonance imaging neurofeedback), cognitive-behavioral therapy, and public health policies have shown potential efficacy. Future research should focus on the development of precision medicine strategies and interdisciplinary integrated intervention models.

**Keywords:** Betel nut, addiction, Arecoline, Neurobiological mechanisms, Intervention strategies, Health hazards

**Running Title:** Betel Nut Addiction: Consequences, Neurobiology, and Interventions

## 1 Introduction

*Areca catechu* L., an evergreen tree belonging to the genus *Areca* of the palm family (Arecaceae), is native to Malaysia and is primarily distributed in the tropical regions of Asia, Africa, and Europe<sup>1</sup>. Betel nut (*Areca catechu*), the mature fruit of the *Areca catechu* L., is used as a traditional herbal medicine in South and Southeast Asia, including India, and is one of the four major medicinal plants in southern China, documented in *the Compendium of Materia Medica*<sup>2</sup>. Currently, betel nut as the fourth most commonly used psychoactive substance following tobacco, alcohol, and caffeinated beverages, is widely popular worldwide<sup>3</sup>.

In traditional medical applications, betel nut has been used in China since around 25-220 AD, with traditional uses including the treatment of various diseases such as malaria, diarrhea, ascariasis, edema, food stagnation, arthritis, and beriberi<sup>4</sup>. Betel nut contains diverse bioactive compounds, primarily alkaloids, flavonoids, tannins, terpenoids, steroids, fatty acids, and amino acids. These constituents exhibit multiple biological activities, including anti-inflammatory, antioxidant, neuroprotective, gastrocardiovascular, endocrine, antitumor, and antipathogenic effects<sup>5</sup>.

Low doses of betel nut and its mixtures are traditional Chinese medicines with good clinical efficacy<sup>6</sup>. However, long-term or excessive chewing of betel nut can cause adverse reactions or related malignant diseases in the human body, such as cardiovascular diseases, metabolic syndrome (MetS), and oral cancer<sup>7</sup>. Current research has found that arecoline, the major active component of betel nut, leads to addiction through complex neuroregulation involving the cholinergic, dopaminergic, and glutamatergic systems<sup>8</sup>.

Betel nut addiction poses a significant threat to public health. Although current interventions for betel nut addiction, which cover pharmacotherapy, neuroregulation techniques, cognitive-behavioral therapy, and public health policies, have made some progress, many challenges remain. This review aims to summarize the latest research progress on the epidemiological characteristics, health hazards, neurobiological mechanisms, and intervention strategies of betel nut addiction, to provide guidance for future research directions, and contribute wisdom and strength to addressing the global public health issue of areca nut addiction.

## 2 The Prevalence and Harm of Betel Nut Addiction

## 2.1 Epidemiological Characteristics

Betel nut is the fourth most popular psychoactive substance in the world, after tobacco, alcohol, and caffeinated beverages<sup>8</sup>. The prevalence of betel nut use exhibits distinct geographical and cultural variations. According to numerous epidemiological studies, approximately 600 million people worldwide chew betel nuts<sup>9</sup>, predominantly in South Asia, East Africa, and the Western Pacific region<sup>10</sup>. The lifetime prevalence of betel nut chewing in the Taiwan region is 15.6%, while in Nepal it is 43.6%. Men in the Eastern and South Asian study communities were deemed likely to combine chewing with smoking and drinking (5.6-13.6%)<sup>11</sup>. India, the world's largest consumer of betel nuts, has about 23.9% of its adult population using betel nuts, which amounts to approximately 223.79 million people<sup>12</sup>. It is worth noting that high usage rates are also maintained in immigrant communities. For example, the rate of betel nut use among South Asian immigrants in the UK is about 15-20%<sup>13</sup>.

Betel nut use shows significant gender/age disparities: male prevalence is 3-5 times higher than female in endemic regions, likely reflecting sociocultural restrictions on women's psychoactive substance use<sup>14</sup>. In terms of age distribution, betel nut use typically begins in late adolescence (15-18 years) and peaks in the 20-40 age group<sup>15</sup>.

Socio-environmental factors strongly influence betel nut use, with notably elevated prevalence among workers in physically demanding or sustained-alertness occupations (e.g., construction, truck/taxi driving)<sup>16</sup>. These individuals often use betel nut as an anti-fatigue agent. Data from Taiwan and India indicate that betel nut use is more prevalent among individuals with lower levels of education, higher levels of stress, and poorer family incomes<sup>17,18</sup>. This association likely reflects multiple mechanisms: betel nut's low-cost accessibility (processed betel nut snacks are commonly found in convenience stores on street corners, small grocery stores, supermarkets, and other retail outlets), its use as a stress-coping mechanism amid high life pressures, and limited health literacy regarding its harms among these groups<sup>19</sup>.

In recent years, the prevalence trend of betel nut use has seen some new changes. Recent trends show betel nut product diversification (e.g., packaged nuts, gum) attracting youth<sup>15</sup>, while targeted interventions (such as the "Betel Nut Harm Prevention Regulations" in Taiwan) reduced overall prevalence<sup>20</sup>. Therefore, the future trend of betel nut use also depends on the tension between the drivers of cultural diffusion and public health containment measures. However, persistently high usage in underregulated areas remains a critical public health challenge<sup>21</sup>.

## 2.2 Health Hazards

### 2.2.1 Oral Diseases

Long-term chewing leads to oral submucous fibrosis (OSF), an oral potential malignant disorder with an approximately 6% transformation rate to oral squamous cell carcinoma (OSCC)<sup>22</sup>. As shown in Figure 1, India has the highest prevalence of OSF at 4.0%, followed by Indonesia at 3.0%, China at 2.1%, Sri Lanka at 1.6%, Saudi Arabia at 0.5%, and the United States has the lowest prevalence at only 0.3%<sup>23</sup>. Epidemiological evidence also demonstrates that the use of betel nut is a significant risk factor for the development of oral leukoplakia and lichenoid oral mucosal lesions<sup>24</sup>. The most definitive health hazard of betel nut is its carcinogenicity<sup>25</sup>. Epidemiological studies consistently demonstrate a significant correlation between betel nut use and the incidence of oral cancer, with approximately 50% of oral cancers being caused by betel nut chewing<sup>26</sup>. The polyphenolic compounds and arecoline present in betel nut can form reactive oxygen species (ROS) under alkaline conditions (after the addition of lime), which directly damage DNA<sup>27</sup>. Molecular biological studies have demonstrated that betel nut extracts can upregulate the expression of oncogenes such as Asb6, thereby promoting abnormal cell cycle proliferation<sup>28</sup>. A hospital-based matched case-control study found that the synergistic combination of betel nut chewing, smoking, and alcohol consumption was strongly associated with an increased risk of oral cancer, showing a 123-fold higher incidence compared with abstainers (95% CI 17.1 – 880.5)<sup>29</sup>. Additionally, research has found that betel nut chewing can alter the oral microbiota<sup>30</sup>, leading to dysbiosis and an increase in the number of periodontitis-causing bacteria such as *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia*, which may enhance the susceptibility to periodontitis<sup>31</sup>.

### 2.2.2 Cardiovascular Systems

Betel nut chewing is associated with various cardiovascular diseases and metabolic disorders. Some scholars have assessed the correlation between betel nut chewing and cardiovascular health and found that habitual betel nut chewing is an important cardiovascular risk factor, associated with cardiovascular diseases such as hypertension, atherosclerosis, inflammation, and ischemic heart disease<sup>32</sup>. Studies in rats (intraperitoneal injection of different concentrations of arecoline) have shown that the main target organs of arecoline are the cardiovascular and central nervous systems. It can damage the myocardial structure of the heart, induce cardiotoxicity and apoptosis<sup>33</sup>. By activating the sympathetic nervous system, arecoline can lead to increased heart rate, elevated

blood pressure, and endothelial dysfunction<sup>34</sup>. Moreover, a computational study has suggested that arecoline blocks high-density lipoprotein receptors and inhibits the liver's uptake of low-density lipoprotein, thereby enhancing the formation of atherosclerosis<sup>35</sup>. Its parasympathomimetic effects can also induce coronary artery spasm. Both of these mechanisms increase the risk of coronary artery disease<sup>36</sup>.

#### 2.2.3 Metabolic system

In terms of metabolic effects, betel nut use is significantly associated with obesity (especially central obesity), insulin resistance, and dyslipidemia. A study targeting the population in Taiwan has shown that the risk of developing MetS for betel nut chewers is 1.629 times that of non-chewers<sup>37</sup>. Additionally, betel nut chewing exhibits gender-specific MetS risk: a strong association in women—mechanistically involving oxidative stress, dyslipidemia, and behavior—but no significant link in men, despite other harms like oral cancer<sup>38</sup>.

#### 2.2.4 Liver Diseases

Frequent betel nut chewing is also a risk factor for liver injury<sup>39</sup>. Clinical observations have revealed that in patients with OSF and oral cancer, the groups with a history of betel nut chewing have higher rates of hepatomegaly on liver palpation, indicating the presence of hepatotoxicity<sup>40</sup>. Animal experiments have shown that high doses of arecoline by oral gavage can activate the PPAR signaling pathway, leading to hepatic steatosis, elevated liver function indices, and disrupted hepatic metabolism in mice through mediating oxidative stress<sup>41</sup>. Betel nut chewing is associated with cirrhosis and hepatocellular carcinoma (HCC), interacting with hepatitis B virus (HBV)/hepatitis C virus (HCV) infections. It also dose-dependently increases liver fibrosis risk in non-alcoholic fatty liver disease (NAFLD) patients, potentially exacerbating inflammation and fibrosis via cytochrome P450 (CYP450) modulation, elevated oxidative stress, inflammatory cytokines, and free radicals<sup>42</sup>.

#### 2.2.5 Kidney Diseases

Research has identified that betel nut chewing may be one of the potential risk factors for the high prevalence of chronic kidney disease (CKD)<sup>43</sup>. Proteinuria is an important manifestation of CKD. A cross-sectional study found that betel nut chewing is an independent risk factor for proteinuria in middle-aged men<sup>44</sup>. Regarding the kidneys, betel nut chewers have an increased incidence of

kidney stones. The mechanism may involve arecoline inducing oxidative stress and activating the epithelial-mesenchymal transition, which leads to kidney fibrosis, tubular injury, and promotes the deposition of urinary crystals<sup>45,46</sup>.

#### 2.2.6 Nervous System and Psychological Effects

Neuroimaging studies have revealed the profound impact of betel nut on brain structure and function. Dependents exhibit reduced gray matter volume in the anterior cingulate cortex (ACC), compromised white matter integrity, and abnormal spontaneous neural activity<sup>47,48</sup>. These structural alterations are associated with deficits in executive function, impaired impulse control, and difficulties in emotional regulation<sup>49</sup>. Research indicates that betel nut chewing can affect the central nervous system and may lead to neurocognitive deficits likely related to the action of arecoline<sup>50</sup>. Arecoline acts as a competitive inhibitor of gamma-aminobutyric acid (GABA) and a non-selective nicotinic and muscarinic agonist. Once entering the body, arecoline rapidly crosses the blood-brain barrier and affects the parasympathetic nervous system<sup>51</sup>. In vitro studies have shown that arecoline exhibits neurotoxic effects on PC12 cells, which are associated with excessive endoplasmic reticulum (ER) stress and the production of hydrogen sulfide (H<sub>2</sub>S), potentially contributing to neurodegenerative diseases<sup>52</sup>.

Long-term, high-dose betel nut use may be associated with psychotic symptoms, resolving after cessation but recurring upon reuse, indicating a clinically significant relationship<sup>53</sup>. However, previous studies suggest that in certain contexts, betel nut consumption may exert potential therapeutic effects on symptoms of schizophrenia, primarily attributed to arecoline's capacity to modulate neurotransmitter systems implicated in the disorder<sup>54,55</sup>. There is a lack of large-scale epidemiological studies providing precise incidence rates of psychosis attributable to betel nut use. Therefore, further research is warranted to comprehensively elucidate the relationship between betel nut consumption and psychotic symptoms.

Habitual betel nut chewing may lead to substance use disorder (SUD), here referred to as betel nut use disorder (BNUD). The development of BNUD begins with socio-culturally driven initiation, progresses through neuroactivation by arecoline leading to habituation, tolerance, and craving, and culminates in loss of control over use, with diagnosis based on DSM-5 criteria and specific scales, although its clinical application requires further regional validation and protocol standardization<sup>56</sup>. Betel nut addiction shares a common mechanism with nicotine addiction at the  $\alpha 4^*$  nAChR target. Chronic use induces neuroadaptive changes, and abrupt cessation leads to cholinergic

system dysregulation, potentially resulting in typical substance withdrawal symptoms such as anxiety, restlessness, irritability, and cognitive impairment<sup>57</sup>. Notably, betel nut use is positively correlated with depressive symptoms, with users generally reporting increased negative emotions and reduced extraversion personality traits<sup>58</sup>.

#### 2.2.7 Reproductive System and Perinatal Hazards

Betel nut also exerts reproductive toxicity. In vivo studies have confirmed that arecoline administered by gavage-induced ROS may activate the cellular antioxidant defense mechanisms, induce spermatogenic damage in male rats, and affect sperm count and motility<sup>59</sup>. In vitro studies have confirmed that arecoline exhibits strong toxicity to oocyte maturation, leading to disordered progression of oocyte meiosis and increased ROS, and ultimately resulting in oocyte apoptosis<sup>60</sup>. Moreover, women who chew betel nuts are more likely to experience adverse pregnancy outcomes. Arecoline can cross the placental barrier, resulting in fetal growth restriction, low birth weight, and neurodevelopmental abnormalities<sup>61</sup>. Research has shown that prenatal betel nut use is associated with preterm birth, stillbirth, miscarriage, and low birth weight, and may lead to neonatal withdrawal syndrome, characterized by symptoms such as infant irritability and hypertonia<sup>62</sup>. Animal experiments have shown that prenatal exposure to arecoline can impair learning and memory abilities and induce hyperactive-like behaviors in offspring<sup>52</sup>.

#### 2.2.8 Respiratory System and Other Harms

Betel nut chewing also affects the respiratory system. Betel nut chewing is associated with higher chronic obstructive pulmonary disease (COPD) prevalence, as shown in a Taiwanese population study, potentially via chronic inflammation and oxidative stress<sup>10</sup>. The CHRN4 rs7178270 GG genotype is a risk factor for lung cancer ( $OR = 1.729$ ). The study found a significant multiplicative interaction between this genotype and areca nut chewing: among areca nut chewers, individuals carrying this genotype had a significantly elevated risk of lung cancer ( $OR_{adj} = 3.095$ )<sup>63</sup>. The toxicity of arecoline to lung adenocarcinoma (LUAD) was verified by computer simulation methods and in vitro experiments<sup>64</sup>.

In addition, ultrasound examinations found that the T-score of the calcaneus (a bone density indicator) was significantly reduced in long-term betel nut users, indicating a potential risk of osteoporosis<sup>65</sup>. Table 1 summarizes major health harms of betel nut consumption.

### **2.3 Social Impact**

The socioeconomic burden caused by betel nut-related diseases is substantial and cannot be ignored. In regions where betel nut use is prevalent, such as India and Taiwan, the cost of treating oral cancer accounts for 15-25% of the total expenditure on cancer care<sup>66</sup>. In addition to direct medical costs, productivity losses (due to illness or premature death), the burden of family caregiving and social welfare expenditures also constitute significant economic pressure<sup>21</sup>.

Betel nut use is often associated with marginalized groups, creating a vicious cycle of health inequality<sup>19</sup>. Low-income groups are more susceptible to illness due to betel nut use, and illness further exacerbates their economic difficulties<sup>67</sup>. Studies indicate that the level of dependence among betel nut chewers is comparable to that observed in cigarette smokers<sup>68</sup>. China had one of the highest prevalence of tobacco use among men (50.5% among men aged 15 years and over)<sup>69</sup> and the second-highest lifetime alcohol use disorder (AUD) prevalence, at 13.18% (95% CI: 4.34, 22.02)<sup>70</sup>, the relationship between the two and betel nut chewing is closely intertwined and forms a vicious cycle. This vicious cycle not only increases the public health burden and direct economic losses, but may also negatively impact adolescent groups, fostering future health and addiction issues<sup>71</sup>. Moreover, the development of areca nut as a cash crop has led to its displacement of other crops, such as rice previously cultivated for subsistence, and the introduction of fertilizers and pesticides to improve yields<sup>72</sup>. The environmental impact of betel nut cultivation (such as deforestation and pesticide pollution) is also increasingly drawing attention and has become an important issue for sustainable development<sup>73</sup>.

## **3 The Neurobiological Mechanisms of Betel Nut Addiction**

### **3.1 Active Components of Betel Nut and Their Pharmacological Properties**

Flavonoids, alkaloids, and phenolic compounds are the major secondary metabolites in betel nut<sup>74</sup>. Betel nut's addictive properties primarily stem from bioactive compounds, notably arecoline—the critical component penetrating deep brain regions to drive addiction<sup>75</sup>. Research has shown that muscarine is a prototypical agonist of the acetylcholine receptors that mediate parasympathetic nervous system stimulation. These receptors control various aspects of parasympathetic action and are crucial for cognitive function<sup>76</sup>. Arecoline is a confirmed muscarinic acetylcholine receptor (mAChR) agonist with high affinity for M1-M4 subtypes, particularly the central nervous system (CNS)-associated M2/M3 receptors<sup>77</sup>. This cholinergic activation mediates cortical arousal and

vigilance, eliciting nicotine-like psycho-stimulant effects.

In addition to arecoline, betel nut also contains several other alkaloids, including arecaidine, guvacoline, and guvacine. These substances undergo structural transformation during the chewing process when alkalinized by lime, thereby enhancing their bioavailability and central activity<sup>34</sup>. Behavioral studies and molecular docking suggest that these alkaloids can bind to various mAChRs and stimulate mAChRs in the nervous system, leading to behavioral changes<sup>78</sup>. Notably, modern processed betel nut products often contain added tobacco, flavorings, and other additives, which further complicate their pharmacological effects<sup>79</sup>. The metabolism of arecoline in the body primarily relies on the cytochrome P450 enzyme system (especially CYP2A6 and CYP2E1), with significant inter-individual variations in metabolic rates. This may partly explain the variability in susceptibility to betel nut addiction among different populations<sup>80</sup>.

### **3.2 Neurotransmitter Systems and Reward Pathways**

The dopamine-mesolimbic incentive-reward-reinforcement loop is a hallmark of addiction. The extracellular fluctuations of dopamine in the brain reward system are currently considered one of the primary reasons for arecoline addiction<sup>81</sup>. Some scholars have used a three-stage (collecting components, predicting targets, and analyzing pathways) computer analysis to demonstrate that betel nut can influence dopamine release, transport, metabolism, and reward through nicotinic receptors and its own alkaloids<sup>82</sup>.

In vivo studies have shown that arecoline decreases fecal dopamine precursors (phenylalanine/tyrosine) in mice and inhibits dopamine neurotransmission: suppressing D2 receptor binding, blocking dopamine transporters, reducing striatal dopamine turnover, and causing accumulation—potentially inducing addiction and motor dysfunction<sup>80</sup>. GABA ( $\gamma$ -aminobutyric acid) is the primary inhibitory neurotransmitter in the brain, whose role is to regulate neuronal excitability and maintain the balance of the nervous system. It has been found that repeated exposure to addictive substances can lead to changes in the expression of GABA-synthesizing enzymes (such as GAD67), and alterations in the GABA system may be associated with drug craving and withdrawal symptoms<sup>83</sup>. Animal studies demonstrate arecoline excites VTA dopaminergic neurons, increasing firing and burst rates and enhancing glutamate-GABA signaling—mechanisms potentially contributing to betel nut addiction<sup>84,85</sup>. This dopamine release pattern resembles other stimulants (e.g., cocaine, nicotine) but with lower intensity<sup>85</sup>, possibly explaining betel nut's slower addictive progression.

It is currently believed that glutamatergic dysfunction is the fundamental pathophysiological basis for addictive behaviors associated with various types of psychostimulants<sup>86</sup>. Research has shown that different low-molecular-weight (LMW) compounds in betel nut can activate glutamate receptors, enhancing neuronal excitability and thereby producing feelings of excitement and pleasure. This neuroexcitatory effect is likely one of the important mechanisms underlying betel nut addiction<sup>87</sup>. Two-dimensional proton magnetic resonance spectroscopy (2D<sup>1</sup>H-MRS) reveals elevated glutamate and glutamine complex (Glx)/creatine (Cr) ratios in the bilateral anterior cingulate cortex (ACC) of betel nut addicts versus controls, suggesting betel nut-induced glutamatergic hyperactivation<sup>88</sup>.

Arecoline transiently elevates hippocampal calcium (within 30 min)<sup>89</sup>, enhancing neuronal excitability and synaptic plasticity. This dynamic modulation may facilitate memory/cognition with implications for addictive behavior (Figure 2).

### **3.3 Neuroimaging and Changes in Brain Structure and Function**

Advanced neuroimaging reveals betel nut addiction's neural basis: structural magnetic resonance imaging (sMRI) shows reduced cortical thickness, particularly in the right middle frontal gyrus of the prefrontal cortex (PFC), correlating negatively with addiction severity<sup>90</sup>. Further cortical thickness analyses have confirmed that chronic betel nut chewers have thinner bilateral dorsolateral prefrontal cortices and reduced gray matter volume<sup>91</sup>. Functional magnetic resonance imaging (fMRI) indicates significant functional abnormalities in the prefrontal cortex of betel nut addicts. For example, during cue-reactivity tasks, betel nut addicts show significantly higher responses in the right ventromedial PFC, left posterior cingulate cortex (PCC), left parietal lobe (LPL), left middle temporal gyrus, and left visual cortex compared to control subjects<sup>92</sup>. It is hypothesized that the reduced PFC thickness and functional abnormalities may affect the retrieval of reward-related memories associated with betel nuts, thereby influencing the decision-making process regarding whether to continue chewing betel nuts and perpetuating addictive behavior.

Resting-state functional magnetic resonance imaging (rs-fMRI) has revealed abnormal brain functional connectivity in individuals with betel nut addiction<sup>93</sup>. Studies have shown that in betel nut addicts, neural activity and functional connectivity are reduced in executive control regions such as the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC)<sup>94</sup>, as well as in reward and cognitive control regions, including the left lentiform nucleus, left insula, and the right caudate-right DLPFC connection within the fronto-striatal circuit<sup>95,96</sup>. Conversely, functional

connectivity is significantly enhanced in regions such as the orbitofrontal cortex, inferior temporal gyrus, and angular gyrus, which may be associated with craving and impulsive decision-making in betel nut addicts<sup>97</sup>. Some researchers have also found that the network switching rate in betel nut addicts is positively correlated with the severity of addiction<sup>98</sup>, although this correlation is attenuated after controlling for confounding factors, suggesting that further exploration with larger samples may be needed in the future.

Magnetic resonance spectroscopy (MRS) studies have provided neurochemical evidence of betel nut addiction. In the anterior cingulate cortex of betel nut dependents, decreased levels of  $\gamma$ -aminobutyric acid (GABA) and increased glutamine/glutamate (Glx) ratios are observed, indicating a disruption of the inhibitory/excitatory balance that is associated with impulsivity and emotional regulation disorders<sup>88</sup>.

### 3.4 The Role of the Microbiota-gut-brain axis

The dynamic bidirectional communication of the “gut-brain axis” has emerged as a research hotspot in the field of drug addiction<sup>99</sup>. The gut microbiota can modulate brain function by stimulating neuronal responses (such as via the vagus nerve) or by secreting metabolites that directly influence brain behavior<sup>100</sup>. Therefore, gut microbiota dysbiosis is one of the etiopathological factors in many metabolic, psychiatric, and neurodegenerative diseases.

As shown in Figure 3, both animal and clinical studies have found that betel nut use significantly reduces the  $\alpha$ -diversity of the gut microbiota, leading to overgrowth of the genus Prevotella and a decrease in short-chain fatty acid (SCFA)-producing bacteria<sup>101</sup>. This microbial imbalance affects brain function through several mechanisms: First, it reduces the production of beneficial metabolites (such as butyrate), thereby weakening their protective effect on the blood-brain barrier<sup>102</sup>. Second, it increases gut permeability, activates inflammatory signaling pathways, and enhances blood-brain barrier permeability, thus affecting brain angiogenesis and inducing neuroinflammation<sup>103</sup>. Third, it influences the brain's reward system, increasing susceptibility to drugs and promoting drug addiction<sup>104</sup>.

New research evidence indicates that the impact of gut microbiota on tryptophan metabolism and the serotonergic system is crucial within the “gut-brain axis.” Tryptophan in the human body is primarily metabolized through two pathways: the serotonin pathway and the kynurene pathway. The former's main metabolite, 5-hydroxytryptamine (5-HT), regulates mood, behavior, and cognitive function, while the latter's metabolites, such as quinolinic acid, are neurotoxic<sup>105</sup>.

Therefore, imbalances in tryptophan metabolism are often associated with negative emotions like depression and anxiety and may be an important driver of mood disorders during withdrawal and relapse<sup>106</sup>. Animal experiments have shown that probiotic supplementation (e.g., Lactobacillus) can partially correct this metabolic disorder, producing short-chain fatty acids (SCFAs) with various positive effects on the central nervous system (CNS) together with a healthy gut microbiota, thereby reducing betel nut-seeking behavior<sup>107</sup>.

Studies have also found that arecoline disrupts the “gut-liver-brain axis”, elevating hepatic dopamine while reducing cerebral 5-HT. This implies altered hepatic metabolism/immunity and potential CNS modulation via neurotransmitter shifts<sup>108</sup>. This multi-organ interaction forms a vicious cycle of “betel nut-gut-liver-brain,” which not only sustains the state of addiction but also exacerbates the multisystem toxicity of betel nut.

### **3.5 Immune Inflammation and Oxidative Stress**

Research has confirmed that inflammatory and immune-related processes may affect the central nervous system by altering the blood-brain barrier (BBB) and modulating the function of normally immunocompetent brain cells, such as astrocytes and microglia. This can even impair neuronal development and homeostasis<sup>109</sup>. Neuroinflammation is currently considered a key factor in addictive behaviors. Addictive substances may activate the Toll-like receptor 4 (TLR4)/NF-κB signaling pathway, leading to the substantial release of pro-inflammatory cytokines (such as TNF-α, IL-6, and IL-1β). This induces inflammatory processes in the mesocorticolimbic circuitry, contributing to the maintenance of addictive behaviors<sup>110</sup>.

Inflammatory processes can induce oxidative stress and mitochondrial dysfunction, thereby exacerbating oxidative stress and triggering negative feedback loops, which lead to downstream abnormalities in brain development and functional impairments<sup>111</sup>. In vitro experiments have shown that arecoline increases intracellular ROS levels and Ca<sup>2+</sup> concentrations in HT22 cells (mouse hippocampal neuronal cells) in a dose-dependent manner. This stimulates endoplasmic reticulum stress (ERS) and the expression of ERS-related apoptotic proteins, resulting in cellular neurotoxicity<sup>50</sup>. The compensatory upregulation of antioxidant defense systems is often insufficient to counteract the oxidative burden caused by chronic betel nut chewing, leading to persistent oxidative damage<sup>112</sup>.

### **3.6 Genetic Susceptibility Factors**

Given limited direct evidence on areca nut addiction's genetic basis, this paper proposes informed hypotheses derived from two sources: the neuropharmacology of its active components (e.g., arecoline) and genetic insights from other substance addictions. Based on shared neurobiological mechanisms of addiction, we suggest that relevant gene polymorphisms may similarly confer genetic risk for areca nut dependence. Thus, this study integrates these perspectives to build a theoretical framework guiding future research on its genetic susceptibility.

Epigenetic modifications (DNA methylation, histone modification, non-coding RNAs) mediate betel nut addiction by regulating gene expression networks. This alters neurobiological processes—synaptic plasticity, neuroinflammation, behavioral adaptation—without changing DNA sequences<sup>113</sup>.

Through genome-wide DNA methylation analysis, studies have identified 186 promoter regions with CpG sites that exhibit either hypermethylation or hypomethylation in addicted individuals compared to healthy controls<sup>114</sup>. The functions of these genes are primarily related to synaptic transmission and neurodevelopment, which are consistent with the neurobiological underpinnings of behavioral addiction.

Histone modifications include histone acetylation and methylation. A key gene regulated by histone modifications is Fosb. The epigenetic activation of Fosb and the increase of its truncated splice variant  $\Delta$ Fosb may accumulate under chronic stress, thereby reducing plasticity, inducing cognitive rigidity, and promoting compulsive behaviors, which are hallmarks of addiction<sup>115</sup>. Studies have found that an imbalance between histone acetyltransferases (e.g., cAMP response element-binding protein) and histone deacetylases, as well as hyperacetylation of histones (H3 and H4) in the nucleus accumbens, can facilitate the rapid expression of related genes, leading to addiction<sup>116</sup>.

Gene polymorphisms modulate susceptibility to betel nut addiction and treatment response. The dopamine receptor D2 (DRD2) variants associate with addiction-related behavioral phenotypes, particularly the Taq1A1 allele—a reward-processing risk allele linked to heightened craving and withdrawal severity in carriers (Figure 4)<sup>117</sup>.

RNA sequencing reveals arecoline significantly alters hippocampal gene expression—particularly in synaptic plasticity, calcium signaling, and metal ion transport pathways—potentially modulating neuronal excitability and synaptic function to drive addiction mechanisms<sup>89</sup>. Table 2 summarizes multisystem mechanisms and key targets of betel nut addiction.

## 4 Intervention Strategies for Betel Nut Addiction

### 4.1 Pharmacological Treatments

Currently, there are no established pharmacotherapeutic options to alleviate withdrawal symptoms for betel nut dependent individuals seeking to reduce or cease use, as this area of research remains in the experimental stage.

Muscarinic receptor antagonists constitute core pharmacotherapy for betel nut addiction, targeting arecoline's primary actions. However, the muscarinic activity of arecoline stands out. Using nicotine gum or similar products incorporating substitute safe muscarinic agents may help areca nut users to alleviate nicotine cravings/withdrawal, facilitating cessation<sup>76</sup>. Given the potential overlap in neurobiological mechanisms between areca nut and nicotine, understanding pharmacotherapies available for tobacco cessation would be valuable before advancing areca nut cessation therapies<sup>118</sup>. For instance, partial nicotine receptor agonists such as varenicline increased long-term smokeless tobacco (ST) cessation by 34%, whereas it more than doubled cessation rates in smokers (131% increase; RR 2.31, 95% CI 2.01 to 2.66)<sup>119</sup>. It may demonstrate some efficacy in mitigating areca nut addiction, though further research is still required.

Regulating the dopaminergic system is another significant focus. A preclinical study found that antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs), can reduce betel nut consumption in mice and diminish the early symptom of OSF. The former has a long-term impact on reducing betel nut intake, potentially linked to the interaction of dopamine and the release of serotonin in the brain<sup>120</sup>. Clinical evidence indicates antidepressant treatment reduced the clinical severity of betel nut use, as measured by the total amount consumed, frequency of consumption, and SUSRS (BQ) scores. After antidepressant therapy, the addictiveness of betel-nut was significantly reduced by 4 times<sup>121</sup>. Currently, some scholars suggest that SSRIs and MAOIs could serve as first-line pharmacotherapy for betel nut withdrawal, with phenelzine (non-selective MAOI) and St. John's wort as second-line options. However, phenelzine carries significant side effects, while St. John's wort demonstrates suboptimal efficacy<sup>122</sup>. Unfortunately, there are currently no established guidelines or protocols that provide a unified consensus on pharmacological interventions for betel nut cessation. For individuals with concurrent nicotine addiction, using the alternative antidepressant bupropion may be a more effective strategy, as it has additional indications as a smoking cessation aid<sup>87</sup>. However, the evidence base from cessation trials employing pharmacological agents for areca nut addiction is

limited.

Amantadine and memantine, as glutamate receptor modulators, have shown efficacy in reducing cravings, consumption, and the severity of withdrawal symptoms; however, healthcare professionals must evaluate the risks and benefits of long-term treatment while remaining vigilant about the potential for drug abuse<sup>123</sup>.

Anti-inflammatory and antioxidant treatments target the pathophysiological processes associated with betel nut addiction. Research indicates that curcumin has potential as a multifaceted neuroprotectant, influencing serotonergic and dopaminergic signaling pathways, and alleviating neuronal damage, oxidative stress, inflammation, and apoptosis induced by addictive substances<sup>124</sup>. Moreover, antioxidants such as resveratrol, blueberry polyphenols, sulforaphane, and salvianolic acid have been demonstrated to counteract neuroinflammation and degenerative changes induced by addiction by promoting autophagy or enhancing neurogenesis in the adult brain<sup>125</sup>. However, there are no definitive clinical trials to test the efficacy of the aforementioned approaches for areca nut addiction, which provides clear directions for future research.

Traditional Chinese medicine (TCM) formulas and natural products offer unique resources for the treatment of betel nut addiction. Baicalin and baicalein exhibit anti-addiction potential through multi-target actions, including MAO-B inhibition, gut microbiota modulation, and antioxidant effects in animal models<sup>126,127</sup>. The family of tetrahydroprotoberberine alkaloids (THPBs), including l-tetrahydropalmatine (l-THP) and l-stachydrine (l-SPD), acts as D1 receptor agonists and D2 receptor antagonists, influencing dopaminergic pathways and synaptic plasticity, and has shown clinical value in the treatment of substance addiction<sup>128</sup>. Nevertheless, more in-depth studies are necessary.

Astragalus, a dietary herb, positively affects degenerative changes in the neurobiology associated with addiction: its polysaccharides inhibit astrocyte proliferation/microglial activation, reverse mitochondrial damage, and exert antioxidant effects; while astragaloside IV reduces oxidation/apoptosis, regulates calcium homeostasis, exerts anti-inflammatory action, and promotes mitophagy—thereby limiting damaged mitochondrial accumulation and mtROS production<sup>129</sup>. A clinical trial using the "Yilung Sanjie Formula" found that this TCM preparation significantly alleviated withdrawal symptoms associated with betel nut, with mechanisms linked to the remodeling of the lung-gut microbiota<sup>130</sup>. Network pharmacology indicates traditional Chinese medicine (TCM) operates via multi-component/target/pathway mechanisms, which aligns well with the complexity of betel nut addiction. However, challenges such as the standardization

of components and elucidation of mechanisms remain, necessitating more rigorously designed clinical trials for validation<sup>131</sup>.

#### **4.2 Neuromodulation Techniques**

Given the scarcity of direct evidence for neuromodulation interventions in areca nut addiction, this review will approach from the perspective of common neural mechanisms underlying substance addictions to explore the interventional potential of techniques such as transcranial magnetic stimulation and transcranial direct current stimulation, based on theoretical extrapolation and evidence across addiction categories.

Real-time fMRI neurofeedback (rtfMRI-NF) offers a novel intervention for betel nut addiction by enabling direct modulation of reward circuitry—the activation of the nucleus accumbens (NAcc) and the ventral tegmental area (VTA). As an adjunct to therapies like cognitive behavioral therapy (CBT), it trains patients to self-regulate addiction-related brain function—reducing cravings by suppressing target region activation during cue exposure<sup>132</sup>. The unique advantage of this intervention lies in its ability to directly target the neural circuits associated with addiction, avoiding the side effects of pharmacological treatments. However, the high cost of the equipment limits its widespread application.

Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are more economical, non-invasive brain stimulation options. rTMS may treat addiction by modulating reward/executive networks: 10Hz stimulation enhances DLPFC activity (potentially improving executive control and reducing cravings/impulsivity), while suppressing MPFC responses to drug cues<sup>133</sup>. tDCS modulates cortical excitability through weak direct currents, with the most effective protocol involving anodal stimulation of the right DLPFC combined with cathodal stimulation of the left temporoparietal junction<sup>134</sup>. However, the long-term benefits and optimal parameters of these neuromodulation techniques still require further large-scale research.

Deep brain stimulation (DBS) involves the stereotactic surgical implantation of electrodes in specific subcortical brain regions to deliver programmed electrical stimulation. The NAcc is recognized as one of the most successful DBS targets for treating various types of substance addiction<sup>135</sup>. DBS penetrates deeper brain regions than non-invasive therapies (e.g., tDCS), showing promise for severe betel nut addiction. Although clinical DBS studies for betel nut addiction are lacking, preclinical NAcc-DBS in morphine-induced conditioned place preference

(CPP) mice significantly reduced CPP scores—with effects persisting even four weeks post-treatment<sup>136</sup>. Advancing DBS precision and stimulation techniques may clarify its utility for betel nut addiction. However, this will rely on more effective animal models of addiction, including self-administration paradigms and various stimulation patterns, as well as additional preclinical studies to identify the best brain targets and stimulation parameters<sup>137</sup>.

Virtual reality (VR)-neurofeedback integration enables immersive addiction therapy. VR activates addiction memories during reconsolidation windows, reducing cravings via relaxation training<sup>138</sup>. Virtual Exposure Therapy (VET) and Virtual Cognitive Behavioral Therapy (VCBT) allow individuals with addiction to be exposed to virtual environments, gradually decreasing their reactivity to drug cues while helping them learn coping strategies through interactions within the VR setting, ultimately reducing their reliance on substances<sup>139</sup>. This approach enhances ecological validity for skill transfer, though efficacy requires further validation.

#### **4.3 Psychosocial Interventions**

Cognitive Behavioral Therapy (CBT) is foundational for betel nut addiction intervention. Cessation failure primarily stems from low awareness, sociocultural factors, and access barriers. Relapses driven by withdrawal, social cues, and behavior patterns indicate targeted behavioral interventions optimize efficacy<sup>140</sup>. CBT programs tailored to the characteristics of betel nut addiction typically include three core modules: cognitive restructuring (identifying and challenging automatic thoughts that trigger betel nut use), coping skills training (such as distraction techniques), and relapse prevention (analyzing high-risk situations and developing coping plans). The implementation of group CBT among students in Karachi demonstrated that the intervention group had a significantly higher cessation rate (29%) after three months compared to the control group (8%)<sup>141</sup>. The Betel Nut Intervention Trial (BENIT) involved five face-to-face sessions of intensive behavioral intervention over approximately 22 days, resulting in a 72% reduction in betel nut chewing among participants<sup>142</sup>. A systematic review and meta-analysis of 30 studies demonstrated that combining cognitive behavioral therapy (CBT) with pharmacotherapy should be considered the optimal treatment approach for substance use disorders, compared to usual care or pharmacotherapy alone<sup>143</sup>.

#### **4.4 Public Health and Policy Interventions**

Contemporary research delineates betel nut as an independent etiological factor for BNUD<sup>56</sup>.

Consequently, implementing betel nut cessation as a component of primary and secondary prevention is paramount. Such public health initiatives must emphasize targeted interventions at the individual level within a societal context. Crucially, the distinct pathophysiology of BNUD compared to tobacco addiction necessitates the development of a bespoke clinical protocol<sup>144</sup>.

Countries where betel nut chewing is prevalent should implement appropriate policies, education, and cessation programs aimed at controlling its use<sup>145</sup>. In certain states of India, regulations on the ingredients of betel nut products, such as limiting lime content and banning tobacco additives, have also significantly reduced the incidence of OSF. However, the enforcement of these policies often faces resistance from the industry and challenges related to cross-border smuggling, necessitating ongoing regulatory reinforcement<sup>21</sup>. In some regions, such as Australia, betel nut is directly prohibited or restricted from being carried into the country, and possession or sale of betel nut without proper authorization is also illegal. Nevertheless, the widespread availability of betel nut in various Asian grocery stores in Melbourne and on social media platforms across other Australian states indicates a lack of effective regulations for controlling the production and sale of betel nut<sup>146</sup>.

Clinical screening and early intervention can help identify high-risk individuals. Oral mucosal examinations combined with simple questionnaires (such as the "BETEL" tool, which assesses frequency of use, early morning use, tolerance, eye-opener use, and loss of control) have been shown to effectively screen for addiction<sup>147</sup>. Integrating betel nut interventions into primary healthcare systems (such as India's "Oral Health Program") has greatly increased coverage rates<sup>148</sup>. A research team in Hunan Province developed the self-management screening test for betel nut use disorder (SST-BQUD), a 14-item scale covering five domains: subjective cravings (6 items), social consequences of betel nut use (5 items), physical effects of betel nut acids (1 item), oral health impacts (1 item), and psychological/abstinence concerns (1 item). Higher scores on the SST-BQUD indicate more severe symptoms of betel nut use disorder, aiding in data integration, motivating cessation efforts, and providing precise evidence for policy formulation<sup>149</sup>. Supported by local governments, healthcare services, and public media, oral cancer screening interventions have proven successful and can serve as "teachable moments" for implementing betel nut prevention and cessation interventions<sup>150</sup>.

Community empowerment and cultural-economic development address the sociocultural dimensions of betel nut use. Taiwan has designated December 3 as "Betel Nut Prevention Day" to raise public awareness of the hazards of betel nut. In 2019, the Hunan Provincial Betel Nut Food

Industry Management Bureau banned the advertising of betel nut on television and in movies; in September 2021, the National Radio and Television Administration also decided to prohibit promotional activities for betel nut across broadcasting, television, and online platforms<sup>151</sup>. Table 3 summarizes comparison of effects of different intervention strategies.

## 5 Betel Nut Acute Intoxication

Research on acute betel nut intoxication is likely underestimated and insufficient, and its incidence remains essentially unknown. A case of poisoning following betel nut ingestion was reported in Denmark, where a patient developed initial symptoms of coma after consuming a large dose, followed by agitation and self-limited visual disturbances. These manifestations were attributed to cholinergic stimulation<sup>152</sup>. In another case, a patient who had reportedly chewed "King of Betel Nuts" — the upward-growing betel nuts containing higher alkaloid concentrations — presented with disorientation, symmetrically dilated pupils, profuse sweating, warm erythematous skin, and bilateral hand tremors, leading to a diagnosis of sympathomimetic toxicodrome<sup>153</sup>. A review of cases from the Taiwan Poison Control Center revealed that patients with acute betel nut intoxication may present with mild to moderate gastrointestinal, cardiovascular, or neurological symptoms, or develop severe manifestations including coma, hypotension, bronchospasm, respiratory failure, and acute myocardial infarction with cardiac arrhythmias<sup>154</sup>. Currently, the management of acute betel nut intoxication is symptomatic. Supportive care for affected organ systems, rather than specific antidotes, remains the cornerstone of treatment, with close monitoring of vital signs and clinical observation<sup>152,154</sup>.

## 6 Conclusions and Prospects

Betel nut addiction is a complex global public health challenge involving multidimensional factors, including neurobiology, psychosocial aspects, and culture. This review systematically summarizes the epidemiological characteristics, multisystem health hazards, neurobiological mechanisms, and research progress on intervention strategies for betel nut addiction. Betel nut addiction causes multifaceted systemic damage—oral, cardiovascular, metabolic, hepatic, renal, and neurological—while also inducing adverse psychosocial effects. The main active component in betel nut, arecoline, leads to addiction by modulating the cholinergic, dopaminergic, and glutamatergic systems<sup>77,82,87</sup>, and the gut microbiota-brain axis and immune-inflammatory responses also play a part in this process<sup>101,110</sup>. In terms of intervention strategies, pharmacotherapy (e.g., cholinergic

receptor modulators), neuromodulation techniques (e.g., real-time functional magnetic resonance imaging neurofeedback), cognitive-behavioral therapy, and public health policies have shown varying degrees of effectiveness<sup>20,118,132,142</sup>.

Several key scientific questions remain in the field of betel nut addiction research. Current estimates of betel nuts chewers lack a defined timeframe: Do they refer to daily, past-year, or lifetime users? What is the typical single-use dosage? Establishing a clear temporal scope in future work will enhance the data's robustness and utility. The synergistic effects of arecoline and other components are still underexplored, and more experiments are needed to elucidate their combined toxicity mechanisms<sup>27</sup>. The gender differences in betel nut addiction and their neurobiological basis also deserve in-depth investigation<sup>14</sup>. In terms of technological applications, artificial intelligence, and big data analysis are expected to revolutionize the monitoring and intervention of betel nut addiction<sup>139</sup>, while brain-computer interface technology may offer new treatment options for individuals with severe addiction<sup>155</sup>. The translation of basic research to clinical practice requires the conduct of rigorously designed randomized controlled trials<sup>137</sup>, and the scientific validation of traditional medical methods for betel nut withdrawal<sup>118,132</sup>.

Future betel nut addiction research should prioritize: elucidating molecular/neural mechanisms—particularly component synergies—through advanced behavioral models; developing biomarker-guided precision interventions via biobanks and multi-omics data; integrating AI/digital health technologies (such as wearables and XR) with conventional methods to enhance intervention scope/effectiveness; implementing culturally adapted solutions through cross-national collaboration, especially for migrant populations; and advancing policy reforms/industry accountability via graduated regulation and youth prevention education to support cessation and rehabilitation.

The prevention and treatment of betel nut addiction require collaborative efforts from multiple disciplines and departments. By integrating basic research, clinical intervention, and public health strategies, we can reduce betel nut-related harms and improve the quality of life and social functioning of those dependent on it. This is not only an investment in individual health but also an important step towards achieving universal health coverage and sustainable development goals. Future work should establish an international betel nut monitoring network, standardize data collection standards and methods, and consider developing alternative planting plans to reduce the impact on farmers' livelihoods, building a complete intervention chain from prevention to treatment and rehabilitation.

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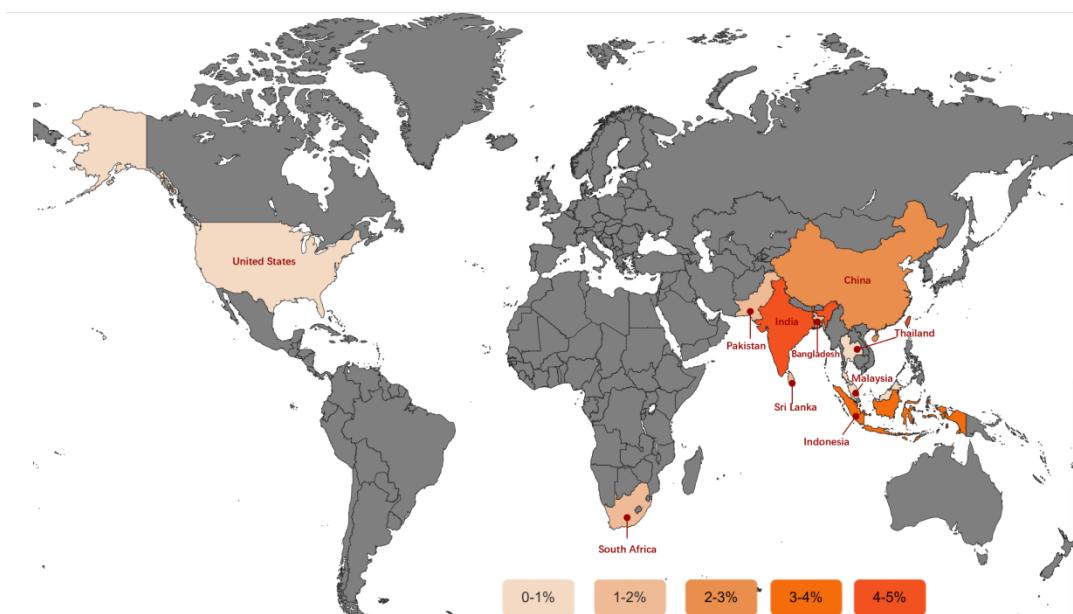
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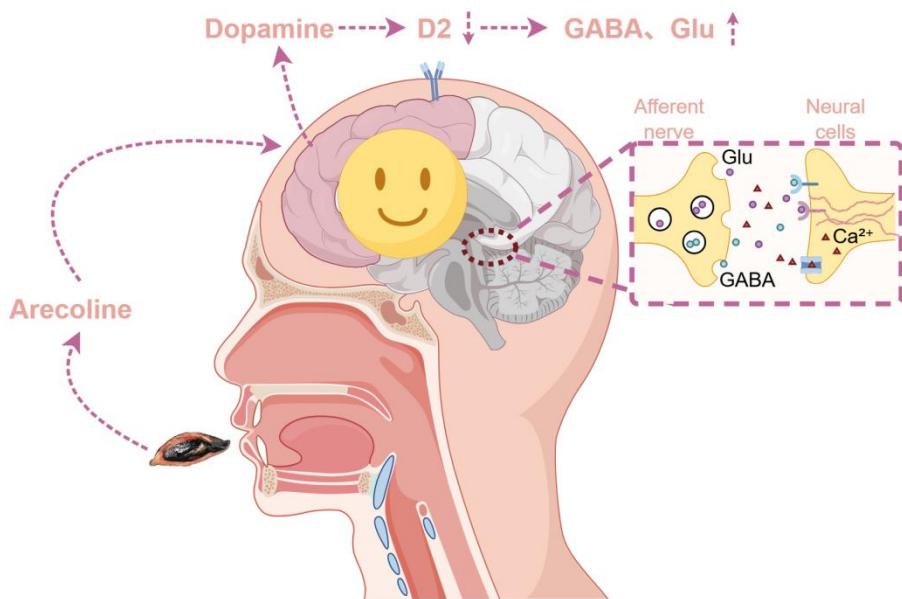
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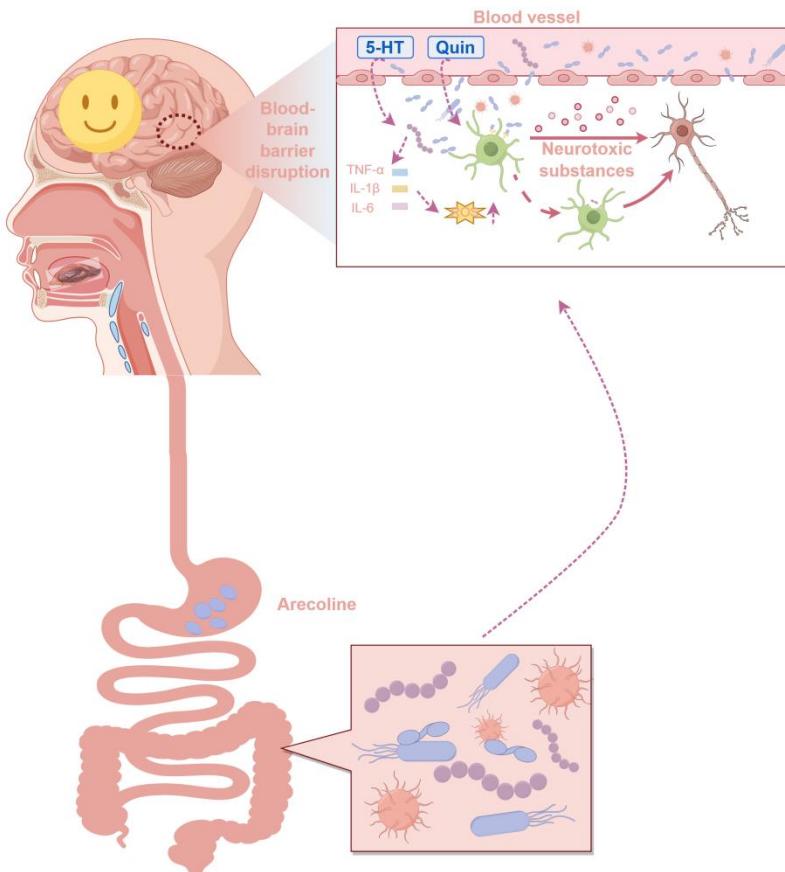
**Figure 1. Worldwide Incidence of Oral submucous fibrosis.**

The incidence of OSF is mainly concentrated in the Asia-Pacific region. The darker the color in the figure, the higher the incidence. India has the highest incidence, up to 4%, and white is the research data without the incidence of OSF.



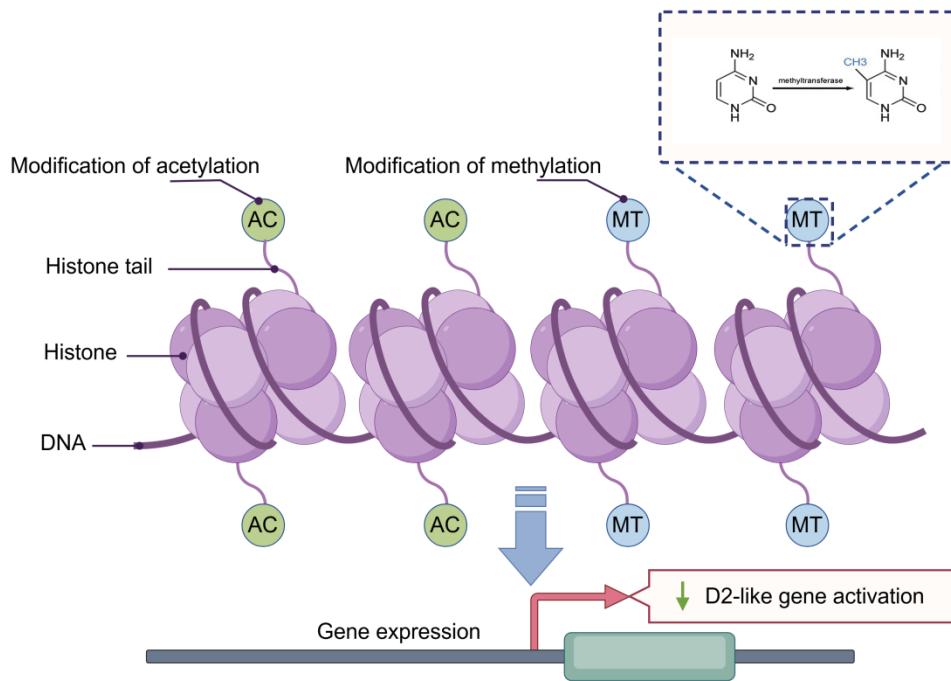
**Figure 2. Neural mechanism of betel nut addiction.**

Arecoline produced by eating areca nut enters the brain, stimulates the production of dopamine in the cerebral cortex, and inhibits the binding activity of D2 receptors to dopamine in the brain, leading to dopamine accumulation. GABA, Glu, calcium signal disorders, enhanced neuronal excitability, produce excitement and pleasure, and affect the memory and cognitive function of the brain, leading to addiction.



**Figure 3. Gut-brain Axis and immune-inflammatory mechanism of betel nut addiction.**

Chewing betel nut affects the brain by affecting intestinal microbes and immune pathways. Microbes and their metabolites (such as 5-HT, quinolinic acid), inflammatory factors (TNF- $\alpha$ , IL-6, IL-1 $\beta$ ) are released through the gut-brain axis, destroying the permeability of the blood-brain barrier, affecting the brain reward system, and promoting drug addiction.



**Figure 4. Epigenetic Regulation of betel nut addiction.**

The whole gene analysis of addiction patients and non-addiction patients found that there were histone modifications in the genes of addiction patients, including acetylation and methylation. These histone modifications can lead to changes in the expression of D2 and other genes, which affect the reward mechanism of the brain and lead to addiction.

**Table 1.** Major health harms of betel nut consumption

<b>Types of Harm</b>	<b>Specific Manifestations</b>	<b>Hazard Ratio (times)</b>	<b>Key Mechanisms</b>
Oral disease	OSF, oral leukoplakia, oral lichenoid lesions, oral cancer, and periodontitis	6-123	DNA damage, chronic inflammation
Cardiovascular system	Atherosclerosis, hypertension	1.02-7	Sympathetic activation, endothelial dysfunction
Metabolic systems	Obesity, insulin resistance	1.60-1.92	Chronic inflammation, oxidative stress
Liver diseases	Liver cancer, cirrhosis, liver fibrosis	1.62-5.69	Oxidative stress, inflammatory response
Kidney diseases	CKD, kidney stones, kidney fibrosis	1.252	Oxidative stress, epithelial-mesenchymal transformation
Nervous system	Deficits in executive function, impulse control disorders, and difficulties in emotional regulation	1.5-2	Neural plasticity changes
Reproductive system	Spermatogenic damage, oocyte apoptosis	-	Oxidative stress
Respiratory system	COPD, pulmonary function decline, lung cancer	1.8	Oxidative stress, inflammatory response

**Table 2.** Multisystem mechanisms and key targets of betel nut addiction

<b>System level</b>	<b>Main pathological changes</b>	<b>Key molecules/pathways</b>	<b>Potential intervention strategies</b>
Neurotransmitter system	<ul style="list-style-type: none"> <li>- Increased dopamine release and downregulation of D2 receptors</li> <li>- Increased GABA levels</li> <li>- Disruption of glutamatergic transmission</li> <li>- Enhanced calcium signaling in the hippocampal region</li> </ul>	<ul style="list-style-type: none"> <li>- Mesolimbic dopamine pathway (VTA→NAc)</li> <li>- GABAergic interneurons</li> <li>- Glutamatergic projections</li> <li>- Calcium signaling pathway</li> </ul>	<ul style="list-style-type: none"> <li>- SSRIs, MAOI</li> <li>- Non-invasive methods (such as transcranial magnetic stimulation or focused ultrasound stimulation)</li> <li>- Glutamate modulators (e.g., amantadine, memantine)</li> </ul>
Brain structure and functional connectivity	<ul style="list-style-type: none"> <li>- Reduced thickness and abnormal reactivity of PFC</li> <li>- Weakened connectivity in the executive control, reward, and cognitive regions</li> <li>- Enhanced connectivity in the impulsivity and decision-making regions</li> </ul>	<ul style="list-style-type: none"> <li>- ACC and DLPFC</li> <li>- Left lentiform nucleus and left insula, frontostriatal circuit</li> <li>- Orbitofrontal cortex, inferior temporal gyrus, and angular gyrus</li> </ul>	<ul style="list-style-type: none"> <li>- Real-time fMRI neurofeedback (targeting the NAcc)</li> <li>- TMS stimulation of the DLPFC</li> </ul>
Microbiota-gut-brain axis	<ul style="list-style-type: none"> <li>- Decreased microbial α-diversity</li> <li>- Increased Prevotella and reduced SCFA-producing bacteria</li> <li>- Tryptophan metabolism shifted towards the kynurenone pathway</li> </ul>	<ul style="list-style-type: none"> <li>- Short-chain fatty acids (butyrate)</li> <li>- Tryptophan-5-HT metabolic axis</li> <li>- Quinolinic acid</li> </ul>	<ul style="list-style-type: none"> <li>- Probiotics (e.g., Lactobacillus) or fecal microbiota transplantation</li> <li>- Butyrate supplements</li> <li>- IDO inhibitors</li> </ul>
Immune inflammatory response	<ul style="list-style-type: none"> <li>- Blood-brain barrier disruption</li> <li>- Microglial activation</li> <li>- Increased levels of</li> </ul>	-TLR4/MyD88/NF-κB signaling pathway	<ul style="list-style-type: none"> <li>- Anti-inflammatory compounds (e.g., curcumin)</li> <li>- N-acetylcysteine</li> </ul>

	TNF- $\alpha$ and IL-6	(antioxidant)
Oxidative stress	<ul style="list-style-type: none"> <li>- Increased levels of ROS and Ca<sup>2+</sup></li> <li>- Endoplasmic reticulum stress (ERS)</li> </ul>	<ul style="list-style-type: none"> <li>- ERS-related apoptotic proteins</li> </ul>
Epigenetic regulation	<ul style="list-style-type: none"> <li>- DNA methylation</li> <li>- Histone modification</li> <li>- <math>\Delta</math>FosB accumulation</li> <li>- DRD2 gene polymorphism</li> </ul>	<ul style="list-style-type: none"> <li>- DNA methyltransferases (DNMTs)</li> <li>- Histone deacetylases (HDACs)</li> <li>- Histone deacetylase</li> </ul>

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**Table 3.** Comparison of effects of different intervention strategies

Type of Intervention	Target Population	Advantage	Limitations	Evidence Level
Cholinergic	Moderate to severe addiction	Target the core mechanism	Common side effects	B
Real-time fMRI neurofeedback	Highly motivated dependent	Fine-tuning neural circuits	High cost, equipment	B
Group cognitive behavioral therapy	Social context users	Skill system training	addiction Long-term persistence	A
Tax policy	The whole crowd	Wide coverage	Industry boycott	A