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Ameliorative Effect of Graviola on Clozapine-Induced Structural Alterations in the Prostate and Seminal Vesicles

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Abstract:

Psychosis is a serious mental disorder characterized by impaired reality testing, hallucinations, delusions, disorganized thinking, and cognitive dysfunction. Antipsychotic drugs remain the cornerstone in the management of schizophrenia, bipolar disorder, and other psychotic illnesses. Clozapine is a second-generation antipsychotic and is considered the gold standard treatment for treatment-resistant schizophrenia because of its superior efficacy in improving positive, negative, and cognitive symptoms, as well as reducing hospitalization and suicide risk. However, its clinical use is limited by several adverse effects, including agranulocytosis, seizures, myocarditis, metabolic disturbances, and possible urogenital side effects related to anticholinergic and α-adrenergic receptor blockade. These effects may influence prostate and seminal vesicle function, although this area remains insufficiently studied. Graviola (Annona muricata) is a medicinal plant rich in flavonoids, acetogenins, alkaloids, and phenolic compounds, with documented antioxidant, anti-inflammatory, antimicrobial, anticancer, and tissue-protective properties. Its ability to reduce oxidative stress and modulate inflammatory pathways suggests a potential protective role against drug-induced tissue injury. Therefore, studying the possible ameliorative effect of graviola on clozapine-induced histological changes may provide useful insight into protective strategies against reproductive or urogenital toxicity.

Keywords: Clozapine; Graviola; Antipsychotic drugs; Prostate; Seminal vesicles; Oxidative stress; Histology.

Introduction:

Psychosis is characterized by disruptions in thought processes, hallucinations, delusions, and impaired reality testing. It affects approximately 3% of the global population and is a hallmark of schizophrenia, bipolar disorder, and severe depression (**1**).

Psychosis includes positive, negative, and cognitive symptoms. Positive symptoms represent pathological excesses or distortions of normal functions, including hallucinations, delusions, and disorganized speech or behavior. Negative symptoms reflect deficits or diminutions of normal functions, such as diminished emotional expression, reduced motivation, loss of pleasure, and asociality. Cognitive symptoms involve impairments in neurocognitive domains like attention, working memory, processing speed, verbal learning, and executive function, which significantly impact daily activities **(2**).

Antipsychotic drugs

Antipsychotic drugs, categorized into typical first- generation and atypical second- generation agents, remain cornerstone treatments for schizophrenia, bipolar disorder, and other psychotic conditions. Typical antipsychotics, such as haloperidol, primarily antagonize dopamine D2 receptors, reducing positive symptoms like hallucinations and delusions. Atypical antipsychotics, including clozapine and risperidone, target serotonin 5-hydroxytryptamine

receptor 2A (5-HT2A) receptors alongside dopamine pathways, offering efficacy for both positive and negative symptoms with a lower risk of extrapyramidal side effects (EPS) **(3)**.

However, atypical antipsychotics can cause side effects like weight gain and dyslipidaemia, so patients need regular monitoring. Guidelines suggest tailoring treatment to each person, balancing benefits and side effects. Clozapine is recommended for resistant schizophrenia because of its superior effectiveness **(4)**.

Despite advancements, disparities in access to antipsychotics persist globally, particularly in low-income regions, highlighting the need for equitable mental health policies and culturally adapted interventions **(5)**.

Clozapine

Clozapine, a second-generation antipsychotic, is the gold standard treatment for treatment- resistant schizophrenia (TRS), defined by inadequate response to at least two other antipsychotics. It is the only antipsychotic proven to reduce suicide risk in schizophrenia and is recommended in international guidelines for TRS due to its superior efficacy in improving positive, negative, and cognitive symptoms (**6)**.

Unlike other antipsychotics, clozapine demonstrates unique effectiveness in reducing hospitalizations and long-term morbidity, with studies showing a 30–50% response rate in TRS populations (**7**).

Clozapine, a tricyclic dibenzodiazepine derivative, has a seven-membered central ring with chlorine substitution that contributes to its distinct receptor-binding profile. Unlike typical antipsychotics, clozapine has broad affinity for multiple neurotransmitter receptors, including serotonin (5-$HT_2A/_3C/_6/_7$), dopamine (D_1/D_4), adrenergic (α_1/α_2), and histamine (H_1) receptors that underpin its atypical properties. This multi-receptor targeting differentiates it from other antipsychotics, enabling efficacy without high D_2 receptor occupancy, which is linked to extrapyramidal side effects (**8).**

Clozapine's therapeutic effects arise from its balanced antagonism at dopamine D_4 and serotonin 5-HT_2A receptors, coupled with partial agonism at 5-HT_1A receptors (figure 1). This modulates mesocortical and mesolimbic dopamine pathways, improving negative symptoms and cognitive deficits while mitigating positive symptoms **(9)**.

Its low D_2 affinity reduces EPS risk, but its strong anticholinergic and antihistaminergic activity contributes to side effects like sedation and weight gain. Additionally, clozapine enhances glutamate transmission in the prefrontal cortex, potentially aiding cognitive recovery (**10)**.

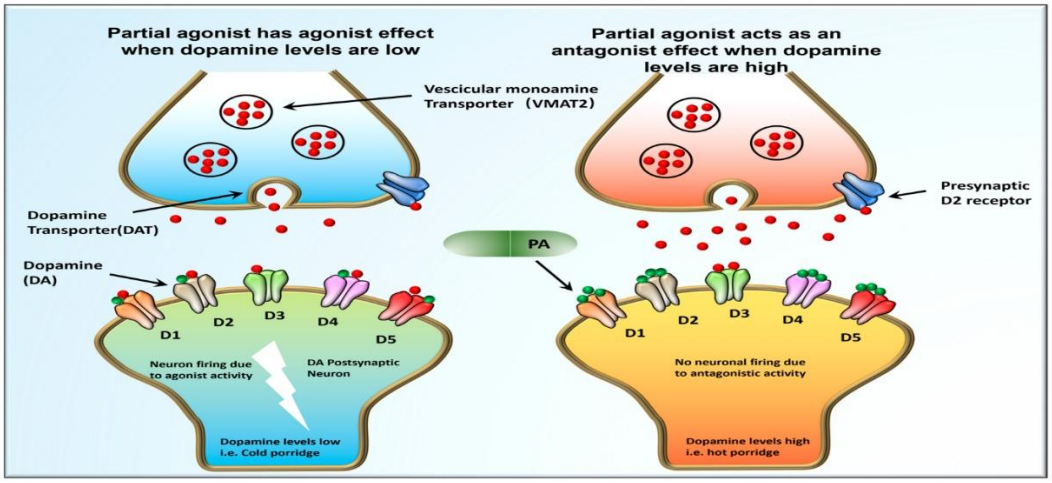

Fig. (1): Dopaminergic pathways between neurons during impulse firing. Partial dopamine receptor inhibitors can adjust dopamine levels in individuals depending on its level in the body at a particular given time **(11)**

Clozapine is available as oral tablets, orally disintegrating tablets, and a suspension. Clozapine is rapidly absorbed orally, with peak plasma concentrations reached in 2 to 4 hours and bioavailability of 60–70% due to first-pass metabolism. It is hepatically metabolized primarily by cytochrome P450 enzymes (CYP1A2 and CYP3A4) into active norclozapine and inactive metabolites. Its half-life ranges from 8 to 16 hours, necessitating twice- daily dosing **(12).**

Clozapine's use requires careful monitoring due to potentially life-threatening adverse effects. Agranulocytosis with a 0.8 to1.3% incidence, necessitates weekly blood monitoring for the first 18 weeks, then monthly indefinitely**.** Other risks include seizures (3–5% at high doses), myocarditis (0.1–1%), and metabolic syndrome. Recent guidelines emphasize baseline cardiac screening and regular metabolic assessments to mitigate risks **(13).**

While the impact of clozapine on the prostate and seminal vesicles remains understudied, its anticholinergic and α-adrenergic receptor antagonism may contribute to urogenital side effects. By blocking muscarinic (M1/M3) receptors, clozapine can theoretically impair smooth muscle contraction in the prostate and seminal vesicles, potentially leading to urinary retention or ejaculatory dysfunction, such as retrograde ejaculation **(14).**

Case reports suggest clozapine may exacerbate benign prostatic hyperplasia (BPH) symptoms due to anticholinergic effects, though direct evidence linking it to structural prostate changes is limited (**15)**.

Additionally, its α1-adrenergic blockade may reduce seminal vesicle contractility during ejaculation, altering semen expulsion. Current guidelines recommend monitoring for urinary symptoms in patients with preexisting BPH but do not necessitate routine prostate screening **(16)**.

Graviola

Graviola, Annona muricata, a tropical evergreen tree native to Central and South America, has garnered significant attention in recent years for its medicinal properties. Traditionally used in folk medicine to treat infections, inflammation, and cancer. Modern scientific inquiry has begun to validate its therapeutic potential (**17)**.

Graviola extracts exhibit significant therapeutic properties for diverse conditions, including wound healing and inflammatory and oxidative diseases and microbial and parasitic infections, as well as chemopreventive and chemotherapeutic effects against cancer.

Studies demonstrate its efficacy in accelerating wound closure through enhanced collagen synthesis and anti-inflammatory activity (**18**), reducing oxidative stress via upregulation of Nrf2 (Nuclear Factor Erythroid 2-Related Factor 2) signaling (**19)**, and combating microbial pathogens such as Staphylococcus aureus and Leishmania parasites (**18**).

Graviola has been traditionally used to treat liver disorders, hypertension, diabetes, and headaches, owing to its hepatoprotective, antihypertensive, and antidiabetic activities. Its parts (leaves, stems, roots, flowers, fruits, and seeds) also possess antidysenteric, antispasmodic, gastroprotective, and antidepressant properties, validated in preclinical models (**20)**. Besides its anticancer potential (**21**) (Figure 2).

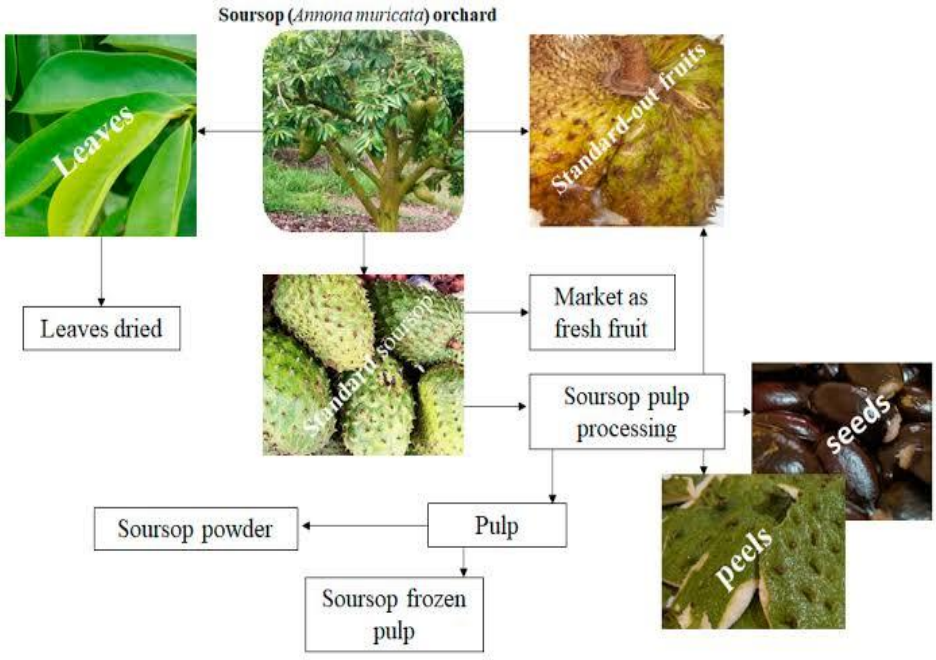

Fig. (2): The soursop production chain **(22)**

Graviola leaves are rich in bioactive compounds, including flavonoids such as quercetin, rutin, and kaempferol, which are known for their antioxidant and anti-inflammatory effects. They also contain acetogenins like annonacin, annomuricin, and muricatocin, which exhibit strong anticancer and antiparasitic activities. Additionally, graviola leaves have alkaloids such as anonaine and asimilobine, linked to neuroprotective and antimicrobial properties (Figure 3). Finally, phenolic acids like gallic and chlorogenic acids contribute to free radical scavenging, enhancing their overall health benefits **(21, 23).**

The mechanisms of action of graviola include ROS scavenging, where flavonoids chelate metal ions and donate hydrogen atoms to stabilize free radicals; apoptosis induction, with acetogenins activating intrinsic apoptotic pathways via cytochrome c release; and immune modulation, as polysaccharides enhance macrophage phagocytosis and natural killer (NK) cell activity **(22).**

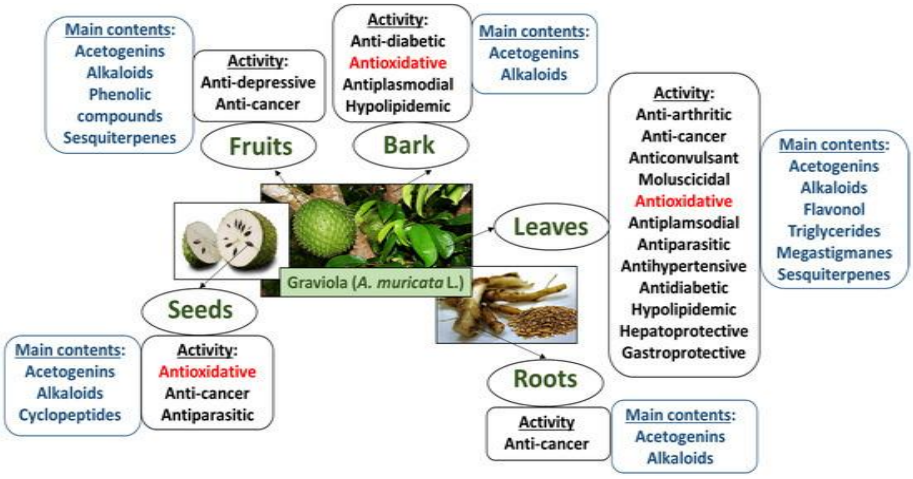

Fig (3): Main contents and main biological properties of various parts of graviola **(23).**

While Graviola is generally safe at therapeutic doses, chronic use of high doses (≥500 mg/kg in rodents) may cause neurotoxicity due to annonacin's inhibition of mitochondrial complex I. Human studies recommend limiting intake to less than 300 mg/day to avoid potential Parkinsonism-like symptoms (**24, 25)**

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