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Review

CHEMICAL AND PHARMACOLOGICAL INSIGHTS INTO THE INDIRECT ANALGESIC MECHANISM OF DEXTROMETHORPHAN VIA NMDA RECEPTOR ANTAGONISM IN CANCER ASSOCIATED PAIN

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Abstract: The This research is based on the analysis of chemical structure and chirality properties and related pharmacological effects on treatment at chemical synapse centers and the central nervous system, as well as pain management by opioid drugs. In this study, we have investigated the chemistry, biochemistry, and medicinal chemistry of the chemical structure of dextromethorphan to provide an in-depth analysis of this compound to answer the ambiguities raised about this compound. The basis of this study is based on an inverse approach that aims to achieve results by examining the therapeutic evidence and chemical properties of

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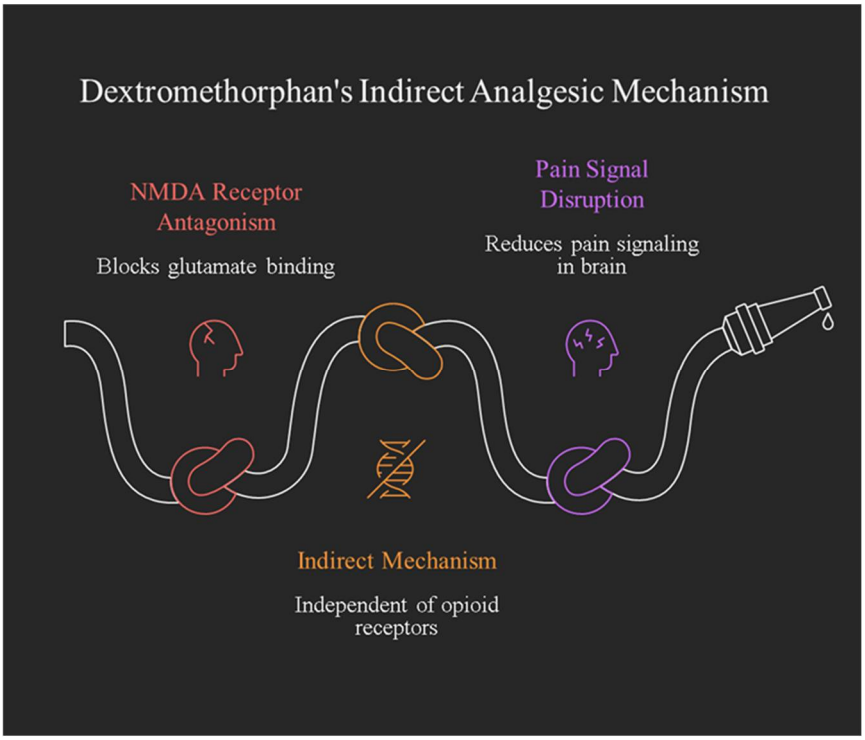
dextromethorphan. This analysis method was first proposed by us and was inspired by the biochemical interactions required in cancer therapy compared to the structural and chemical properties of dextromethorphan and was investigated in this study. A negative answer is decisive and clear, but a positive answer is not as definitive as a negative answer and some factors affecting the answer can be ignored. Dextromethorphan does not activate mu, delta, or kappa opioid receptors. Therefore, it does not have the same analgesic properties as known opioids. But according to this study, which is a review of the relevant scientific literature, dextromethorphan disrupts and blocks the transmission of pain signals in another way, so it is also effective in treating pain and can be recommended for the treatment of cancer. Evidence from various medicinal uses reported in the literature supports this claim. It also simultaneously addresses two related hypotheses about dextromethorphan that have recently been intensively pursued and tested: the use of dextromethorphan in the treatment of codeine and nicotine addiction, and the other in the management of treatment-resistant depression and Alzheimer's disease. The overall goal of this research is to contribute to the social health of human societies.

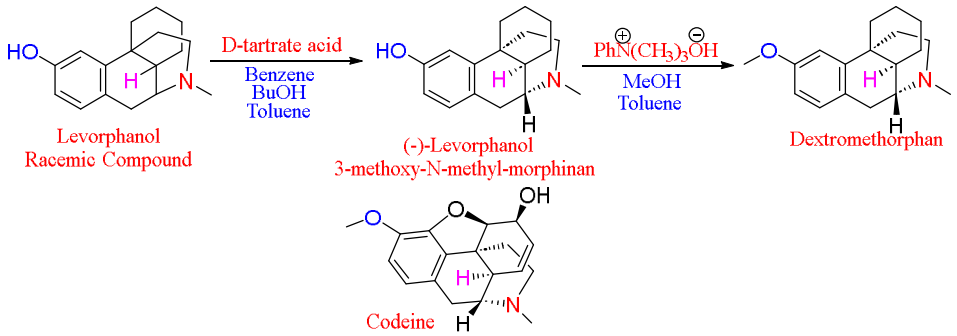
Graphical abstract



***Keywords*:** Opioid Painkillers, Heterocyclic Compound, Glutamic Acid, Antagonist - Painkiller, NMDA Receptor, Nicotrol Chemistry, Cancer, Pain Management

Introduction

More than half a century ago, for the first time in 1949, the synthesis of dextromethorphan as one of the isomers of Levorphanol (Levorphanol with brand name Levo-Dromoran) was reported as a patent.[1] Dextromethorphan, which is under the codeine narcotic category, was first synthesized by chance in the reaction mixture of (-)-levorphanol (3-methoxy-N-methyl-morphinan), (Scheme 1).[2] The structure of codeine is shown in Scheme 1 for comparison with the structure of dextromethorphan.



Scheme 1. The first chemical synthesis presented for the synthesis of dextromethorphan as an analog of Levorphanol and codeine was patented by Roche in 1950.[2-4]

The U.S. Food and Drug Administration (FDA) approved dextromethorphan as a safe and effective antitussive drug in 1958.[2] N-methyl piperidine is N-substituted heterocyclic compound.[5-7] Dextromethorphan is also recognized as an amine heterocycle derivative because of the piperidine ring. These type of amine heterocycles compound can penetrate the central nervous system due to their ability to dissolve in lipid bilayer.[8-10]

Dextromethorphan does not directly affect opioid receptors, so it does not cause side effects of opioids, but because it can affect the N-methyl-D-aspartate (NMDA) receptor, it is known as an antagonist. The NMDA receptor is the receptor for the excitatory neurotransmitter glutamate (Figure 1).[11-13]

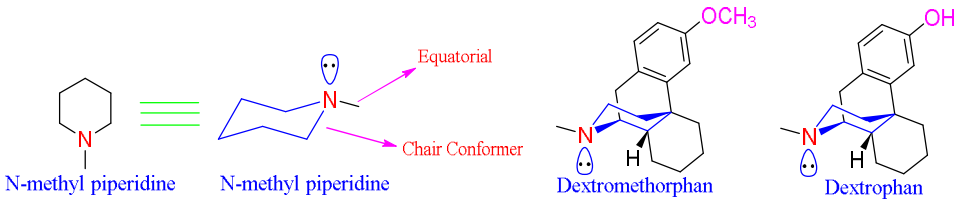


Figure 1. Chemical structures of N-Methyl piperidine, Dextromethorphan, and Dextrophan.

Glutamate or glutamic acid plays an important role in the creation and transmission of nerve messages, such as the formation and transmission of pain messages and the sensation of pain in the brain through chemical synapses.[3, 14] Glutamate plays an important role in the production of another important neurotransmitter called GABA (gamma-aminobutyric acid). Whenever glutamate acts as a stimulus and creates a pain message, GABA acts as an inhibitory or sedative neurotransmitter to alleviate the shock caused by the feeling of pain in response to the pain message in the nervous system. Compounds that have the potential to block the glutamate receptor are effective in creating analgesia and relieving nerve pain. By stimulating the NMDA receptor, dextromethorphan blocks this receptor to bind glutamate (Figure 2).[15-16]

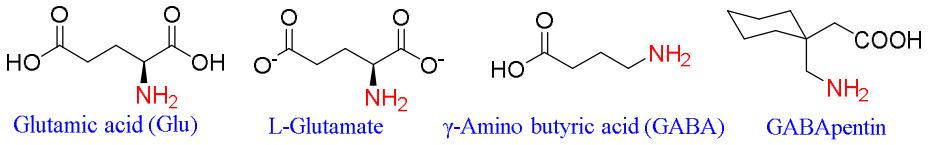


Figure 2. Chemical structure of glutamic acid, glutamate, gamma-aminobutyric acid, and gabapentin.

The chemical compounds having in their structure tetrazoles and carbamates moieties as cyclic amines and acyclic amide can be used in several ways in pain management.[3-7] Firstly, dextromethorphan, as a heterocyclic amine compound, and resonant heterocyclic amine have the potential to enter the central nervous system due to the low polarity of these compounds resulting from the resonance property and the lack of charge

delocalization of the bioisosteric compounds similar to the resonances found in amine acids. Thus, dextromethorphan acts as an NMDA receptor antagonist and may be effective in reducing pain, although it does not directly possess analgesic properties similar to opioids (Figure 3).

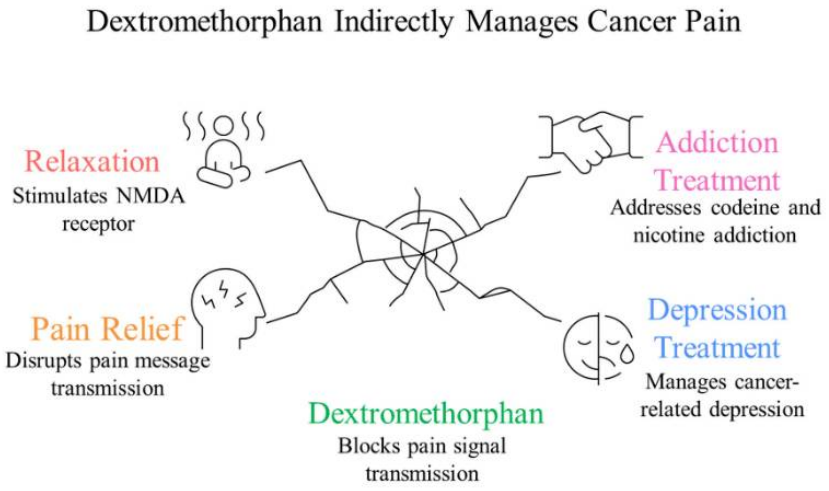


Figure 3. The multifaceted therapeutic potential of dextromethorphan.

This property could lead to the development of new pharmaceutical compounds containing resonant heterocyclic amines that have similar bioisosteric properties, such as tetrazoles and carbamates.[3-7] Secondly, polyaniline as a nanocomposite can be used as a drug carrier for compounds such as dextromethorphan or other new chemical compounds to provide better therapeutic effects in managing pain and other symptoms associated with diseases. Additionally, compounds that can block glutamate receptors are effective in relieving pain, and this is related to bioisosteric properties in compounds such as tetrazoles. Finally, given the above, dextromethorphan could be effective in treating cancer-related symptoms, such as pain management and cough.[3-10]

Critical analysis of dextromethorphan functions

1. Dextromethorphan as an anti-cough agent

Dextromethorphan is a cough suppressant found in many over-the-counter medications used to temporarily relieve coughs caused by the common cold or flu. Dextromethorphan doesn't directly treat the cause of the cough or speed recovery, but it can provide much-needed relief. Dextromethorphan functions by reducing the activity in the part of the brain responsible for triggering coughs.[17-19]

2. Dextromethorphan and diabetes

Dextromethorphan (DXM), which is an NMDA receptor antagonist (i.e., it blocks the effect of a type of neuronal receptor), does not cause or worsen diabetes. Instead, by inhibiting potassium and calcium channels in pancreatic beta cells (the insulin-producing cells of the pancreas; their reduced number or function is the main cause of type 2 diabetes, and they are also destroyed by the immune system in type 1 diabetes), it increases glucose‑dependent insulin secretion. Clinical studies have shown that DXM lowers blood glucose without causing severe hypoglycemia (i.e., an excessively dangerous drop in blood sugar). Furthermore, in animal models, it protects beta cells from death and reduces the risk of diabetes. Therefore, DXM has therapeutic potential.[20-21] The peroxidation of lipids, the disturbance in the balance of various types of nerve mediators such as glutamate, and cytochrome c, and the increase of intracellular calcium cause damage and destruction of neurons, and finally, along with chronic hyperglycemia, kidney injuries, followed by an increase of urea concentration in blood. The nerve cells of the brain are affected and cause cognitive impairment.[22-24]

3. Dextromethorphan as an anti-depressant

The monoamine depression hypothesis simply states that depression is caused by the lack of monoamine neurotransmitters.[25-27] Recent research has shown that dextromethorphan has strong anti-depressant properties. The anti-depressant effect of dextromethorphan is due to its inhibitory effect on the N-methyl-D-aspartate (NMDA) receptor and the nitric oxide-guanosine cyclic monophosphate (NO-cGMP) pathway, (Figures 4 and 5).[28-29] In general, the level of NO was recently reported for a new research combination drug called dextromethorphan-bupropion with multifaceted use in the University of Cambridge for the treatment of major depressive disorder, including treatment-resistant depression, Alzheimer's disease stimulation, and smoking cessation in the final stages of clinical development.[25, 30-34] The primary metabolite of dextromethorphan, Dextrophan, exhibits NMDA receptor antagonistic properties similar to those of phencyclidine and inhibits serotonin reuptake. Therefore, it has a high potential for abuse.

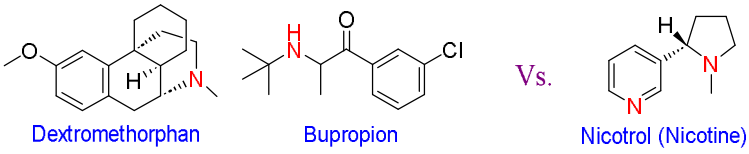


Figure 4. Use of the combination of dextromethorphan and bupropion in nicotine withdrawal.

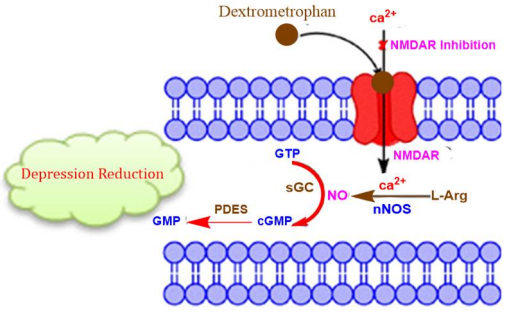


Figure 5. Biochemical mechanism of dextromethorphan antidepressant effect.

3.1. Dual mechanism of action (Antidepressant & Smoking Cessation)

This combination works through different mechanisms:

• ***Antidepressant effect:*** Dextromethorphan is an NMDA receptor antagonist. Bupropion prevents its rapid metabolism and increases its blood levels. This process leads to faster mood improvement than conventional medications.

• ***Smoking cessation aid:*** Bupropion reduces the urge to smoke by inhibiting dopamine and norepinephrine reuptake. Importantly, both substances are direct antagonists of nicotinic acetylcholine receptors; dextromethorphan blocks these receptors, thereby neutralizing the rewarding effect of nicotine. One concern about dextromethorphan is its abuse potential.

However, combining it with bupropion reduces this risk. Bupropion inhibits the metabolizing enzyme CYP2D6, preventing the rapid conversion of dextromethorphan by demethylation, into its hallucinogenic metabolite, dextrorphan, thereby significantly lowering its addictive potential (Figures 4 and 5). This combination offers a novel treatment strategy that simultaneously addresses the two main targets of nicotine addiction (reducing cravings and blocking the reward from smoking) together with a rapid antidepressant mechanism, providing a new dual-purpose treatment tool for smokers who may also suffer from depression.

4. Dextromethorphan in pain management

The isomer D-methorphan (Dextromethorphan) is an analog of codeine, methorphan, and unlike the isomer L-methorphan (Levomethorphan), it does not have analgesic and addictive properties similar to codeine.[11, 35] The

prefixes D and L meaning right and left are taken from the beginning of the words Dexter and Laevus.[11, 36] Dextromethorphan provides pain relief and pain modulation through its ability to act as an antagonist of N-methyl-D-aspartate (NMDA) due to its structure and suitable chemical functional groups, thus disrupting and blocking pain signals, but this effect is not related to the antitussive effect of dextromethorphan.[19, 36-41] This stereospecificity can be the difference between a life-saving drug and a deadly poison. This phenomenon is known as the "role of stereochemistry in biological activity." The main reason this phenomenon is important is because of the three-dimensional interaction of the drug molecule with the body's biological targeted biomolecules. Receptors, enzymes, and proteins in our bodies are themselves chiral: these structures act like a very specific lock that only a specific key (a specific enantiomer) can fit into and open.[42-48] The hand-glove analogy is a very useful example: one enantiomer is like a right hand that only fits into a right-handed glove. The other enantiomer (its mirror image) is like a left hand that never fits into that right-handed glove.

- ***Right-handed enantiomer (Dextromethorphan or DXM):*** It acts mainly on NMDA receptors and has antitussive properties and, at high doses, psychoactive (dissociative) effects. It does not have strong opioid-like properties.
- ***Left-handed enantiomer (Levomorphan):*** It acts mainly on mu opioid receptors (MOR) and is a strong opioid-like analgesic.

Based on the spatial shape of the molecule and the receptors, the difference and mode of action are described below.[49-51]

4.1. Dextromethorphan (Dextromethorphan - right-handed enantiomer)

This enantiomer an active form that's usually found in several cough syrups.

• ***Main mechanism of action:*** Dextromethorphan is an NMDA receptor antagonist. The NMDA receptor plays a key role in the transmission of nerve signals, memory and pain perception. Blocking this receptor leads to an antitussive effect and, at high doses, dissociative effects.

• ***Interaction with opioid receptors:*** Dextromethorphan has almost no significant binding affinity for mu opioid receptors (MOR). This is why it does not exhibit the strong and addictive analgesic properties of morphine.

As a result, the dextro-form fits well into the "hole" of the NMDA receptor due to its special spatial structure, but does not fit into the "lock" of the mu opioid receptor.[49-52]

4.2. Levomethorphan (Levomethorphan - left-handed enantiomer)

This enantiomer is regarded as a potent opioid‑like agent and is not commonly available for routine use.

• ***Main mechanism of action:*** Levomethorphan is a potent agonist of the mu opioid receptor (MOR). This is the same receptor that morphine, heroin, and oxycodone act on.

• ***Interaction with opioid receptors:*** The spatial structure of Levomethorphan (the mirror image of dextromethorphan) perfectly matches the binding site of the mu receptor. This binding causes receptor activation and produces strong analgesic effects, euphoria, and respiratory depression, all of which are characteristics of a classic opioid.

The result is that the left‑handed (Levo) shape acts like a suitable "key" to the "lock" of the mu opioid receptor, thereby exhibiting all opioid‑like properties (Figure 6).[49-51]

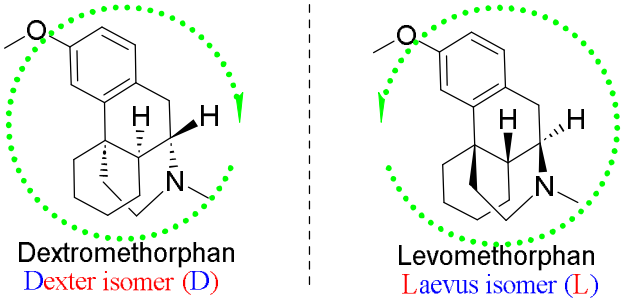


Figure 6. The difference between Dexter (D)- and Laevus (L)- isomers.[11]

Why can dextromethorphan be used in cancer pain management?

As an antitussive (cough suppressant), dextromethorphan primarily targets cough pathways in the brain. It lacks mechanisms that directly target cancer cells or tumor growth pathways, such as inhibiting cell division, inducing apoptosis (programmed cell death), or suppressing angiogenesis (blood vessel formation in tumors). Anticancer drugs typically target specific molecules or pathways in tumor cells, such as key enzymes [e.g., two tyrosine kinases-epidermal Growth Factor Receptor (EGFR), Vascular endothelial growth factor receptor (VEGFR)] or signaling pathways. Dextromethorphan does not interact with these cancer-related targets.[53,54] Dextromethorphan provides pain relief and pain modulation through its ability to act as an antagonist of N-methyl-D-aspartate (NMDA) due to its structure and suitable chemical functional groups, thus disrupting and blocking pain signals, but this effect is not related to the antitussive effect of dextromethorphan (Figure 7).[19, 36-41, 55-60]

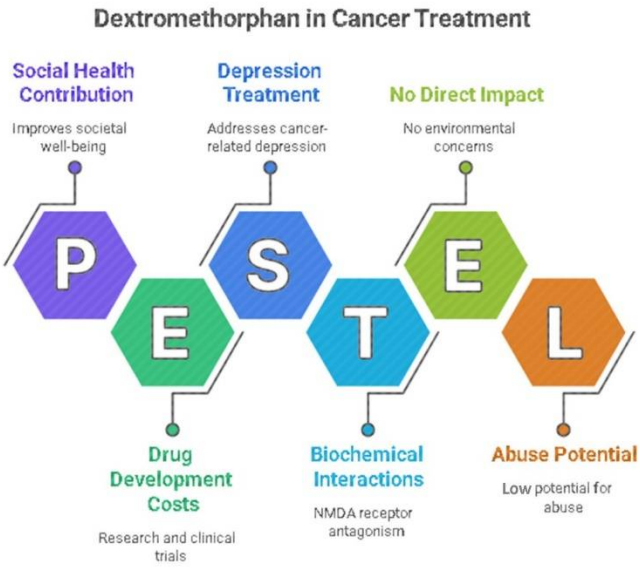


Figure 7. Multifaceted therapeutic profile of dextromethorphan in cancer pain management; P - Pain Management; S - Social Health Contribution; E - Economic and Efficacy; T – Treatment (Therapy); L - Low Abuse Potential (Limited Side Effects).

Conclusions

Dextromethorphan is not an activator or agonist of mu, delta, or kappa opioid receptors; therefore, this isomer does not have the same analgesic properties as known opioids such as codeine, but only disrupts the transmission of pain signals in the nervous system and chemical synapses. While dextromethorphan may help manage cancer-related symptoms (e.g., cough due to airway irritation), its pharmacological properties and mechanism of action preclude it from directly affecting cancer progression or destroying tumor cells. Effective anticancer therapies require precise targeting of cancer-causing mechanisms that fall outside the scope of action of this cough suppressant. However, like opioids, it has a calming effect on the nerves. On the other hand, dextromethorphan stimulates the NMDA receptor and blocks this receptor. In comparison and competition with

glutamate, it disrupts the transmission of pain messages to higher nerve centers and maintains its antagonistic role due to receptor stimulation. Therefore, the biochemical analgesic effect of dextromethorphan is indirectly involved in cancer treatment. It is effective in creating a sense of relaxation. and therefore, it could be an option in treating depression caused by cancer.

Acknowledgments

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Conflict of interest statement

The authors declare no conflict of interest.

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