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The Impact of the Drug Methyldopa in Both Medical and Industrial Applications

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Abstract

Methyldopa is a medication usually used to regulate and treat hypertension. It is one of the most commonly used therapies for high blood pressure during pregnancy. Methyldopa acts on blood vessels by providing additional relaxation, therefor blood can flow more easily through the body. Also, Methyldopa is a common medication used during pregnancy and is unlikely to cause any risk to the baby.

1. Methyldopa

Methyldopa is a medication commonly used to treat hypertension in addition to an anti-Parkinson agent [1] and has been used since the 1960s [2]. It is available under the brand name Aldomet [3]. Methyldopa is a presynaptic α_2-adrenergic receptor agonist, which inhibits norepinephrine release from neurons and, as a result, the sympathetic nervous system. As with many other medications, Methyldopa is effectively carried to the brain as an amino acid and later metabolized to its active form, methylononorepinephrine. In the mechanism of biosynthesis of dopamine, norepinephrine, and epinephrine, methyldopa replaces dihydroxyphenylalanine (DOPA), resulting in the generation of inactive forms of these neurotransmitters. Hence, the signaling pathway from baroreceptors is blocked via methyldopa by changing the solitary nucleus through the above-mentioned inactive neurotransmitters, and stimulation of presynaptic α_2-adrenergic receptors [4]. This drug is often given to people who have heart failure, renal failure, or diabetes. In addition to that, Methyldopa is considered one of the few antihypertensives allowed for pregnancy-induced hypertension [5].

2. Structural Feature of Methyldopa

Methyldopa is a derivative of catechol [3-Hydroxy-α-Methyl-L-Tyrosine]. The chemical formula of methyldopa ($C_{10}H_{13}NO_4$), and its molecular weight (211.21 g/mol), (Figure 1). It is a crystalline powder that can range in color from white to yellowish white or even be colorless. It has no taste or odor and is often dissolved in water [6, 7].

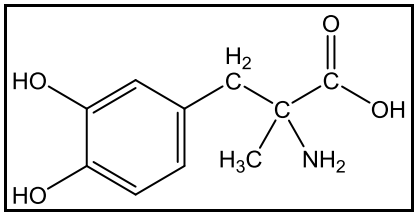
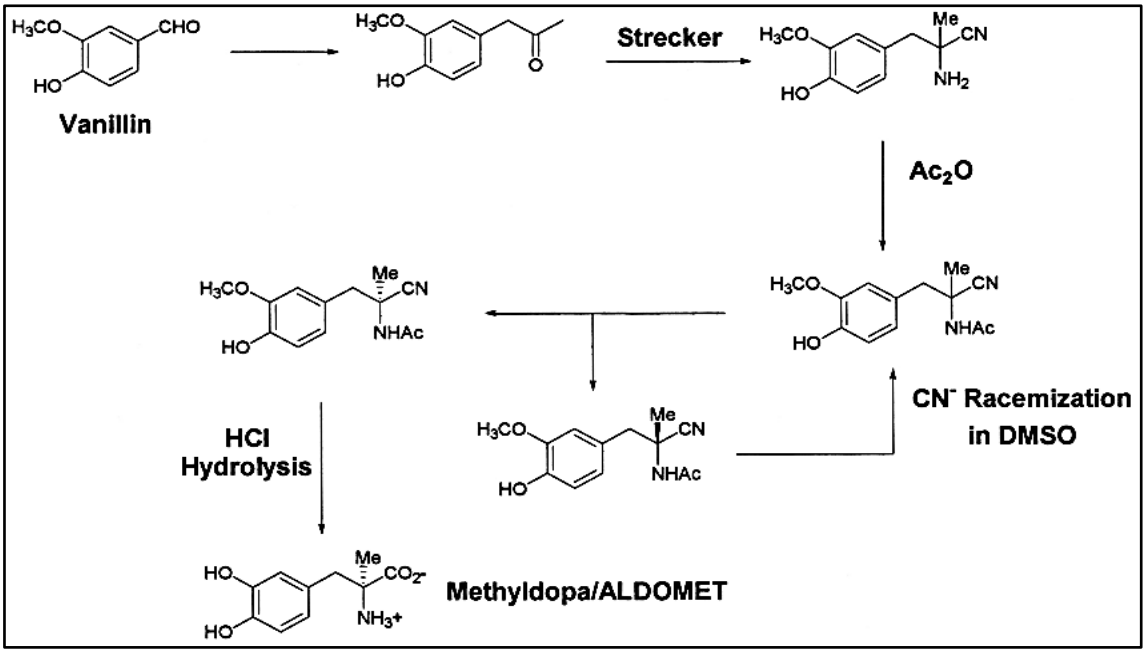


Figure 1. Methyldopa chemical structure.

3. Synthesis of the Drug (Methyldopa)

Methyldopa was manufactured and used a continuous fluidized-bed crystallization resolution racemization method, which, despite being more than 30 years old, remains a great feat in science and technology. Using easily accessible vanillin as a starting point, a simple nitroethane condensation and partial reductive hydrolysis produced methyl vanillyl ketone. The racemic amino nitrile was found by using a typical Strecker reaction (Scheme 1).

However, it was found that an ultimate method could only be reached by including both enantiomers of the amino nitrile in the synthesis. To do this, the nitrile was acetylated, and it was discovered that these intermediate exhibited conglomerate properties that are, the racemate was a physical combination of D and L forms. If a single crystal were extracted from the mixture, it would be enantiomerically pure [8].



Scheme 1. The manufacturing process of methyldopa [7].

4. FTIR Spectrum of Pure Methyldopa Drug

Methyldopa has been characterized by FT-IR spectroscopy device. The FT-IR spectrum showed prominent frequencies at 3475 and 3375 cm^{-1} (for NH_2 stretching vibrations), and 3215 cm^{-1} (for OH stretching vibrations). The ν_{asym} (C=O) of the carboxylic acid group was noticed at 1637 cm^{-1} and ν_{sym} (C=O) 1491 cm^{-1}, 1257 cm^{-1} for (C–N stretching vibration) as illustrated in (Figure 2).

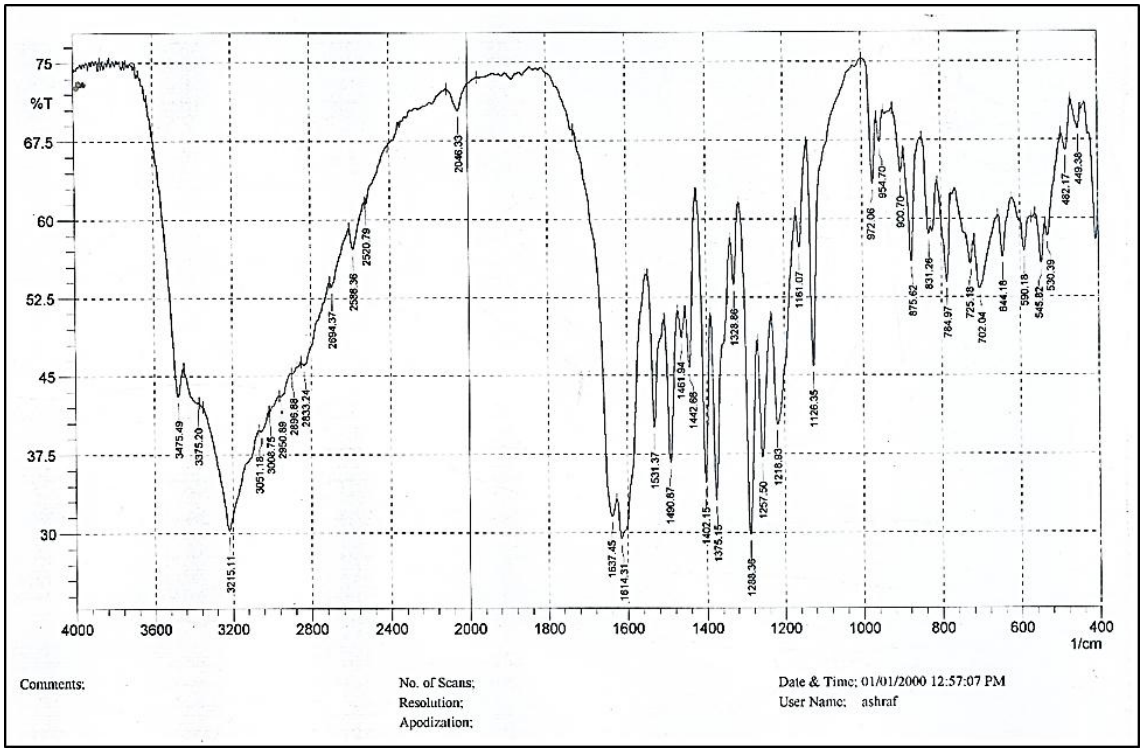


Figure 2. FTIR spectrum of methyldopa (pure).

5. Pharmacology [9]

The action of methyldopa as an antihypertensive is most likely due to the active metabolite, α-methylnorepinephrine. This inhibits adrenergic neuronal influx by serving as something of an agonist at presynaptic α_2-adrenergic receptors inside the brainstem. Blood pressure (BP) is lowered as a result of the attenuated norepinephrine production in the brainstem and decreased outflow of vasoconstrictor adrenergic signals toward the peripheral sympathetic nervous system. Methyldopa decreases supine and standing blood pressure as well as infrequent symptomatic postural hypotension. Methyldopa decreases vascular resistance, has no direct impact on heart function, and often has no effect on glomerular filtration rate, kidney blood flow, or filtration fraction. Plasma norepinephrine concentrations decline in combination with a drop in arterial pressure, which indicates a lowering in sympathetic tone. Despite methyldopa reducing renin secretion, it is not its main mechanism of action. When methyldopa is taken orally, it is absorbed through an active amino acid transporter. The hypotensive impact of a single therapeutic dosage occurs in two or more hours; its greatest effect comes in 6-8 hours, and it remains with declining intensity for 18-24 hours. However, the maximal hypotensive impact from repeated dosages may not occur till the next day. After stopping the medication, the blood pressure recovers to pre-treatment values in 24-48 hours. Methyldopa and its metabolites are eliminated through the kidneys, which have a half-life of about two hours. Methyldopa has actively transferred across the placenta as well as the blood-brain barrier. Methyldopa is also excreted in breast milk; however, amounts are regarded to be too low to damage the infant.

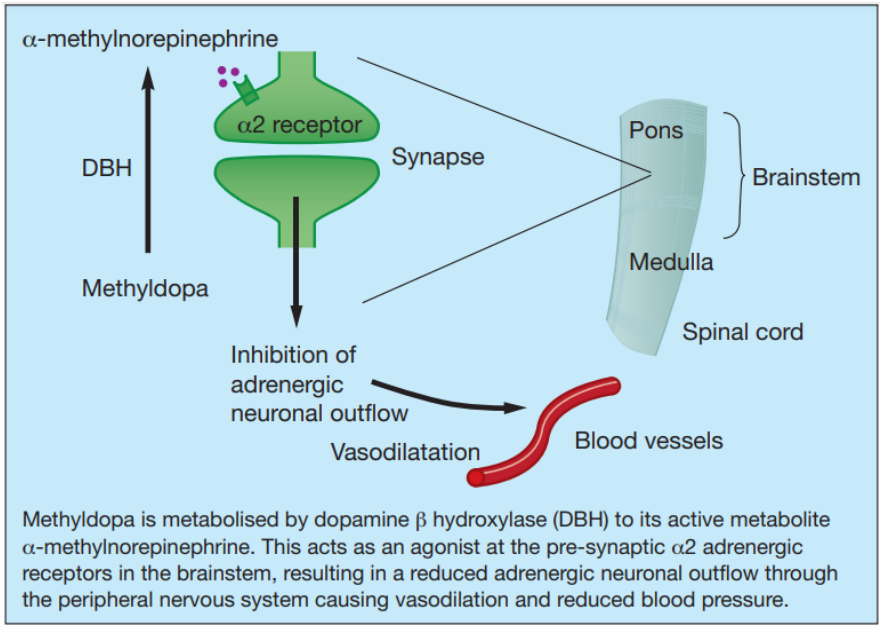


Figure 3. Action mechanism of methyldopa [9].

6. Some Side Effects When Using Methyldopa [10]

Below are the most common methyldopa side impacts on patients.

- Nausea.
- Headache.
- Constipation.
- Diarrhea.
- Nasal stuffiness.

7. Contraindications [11]

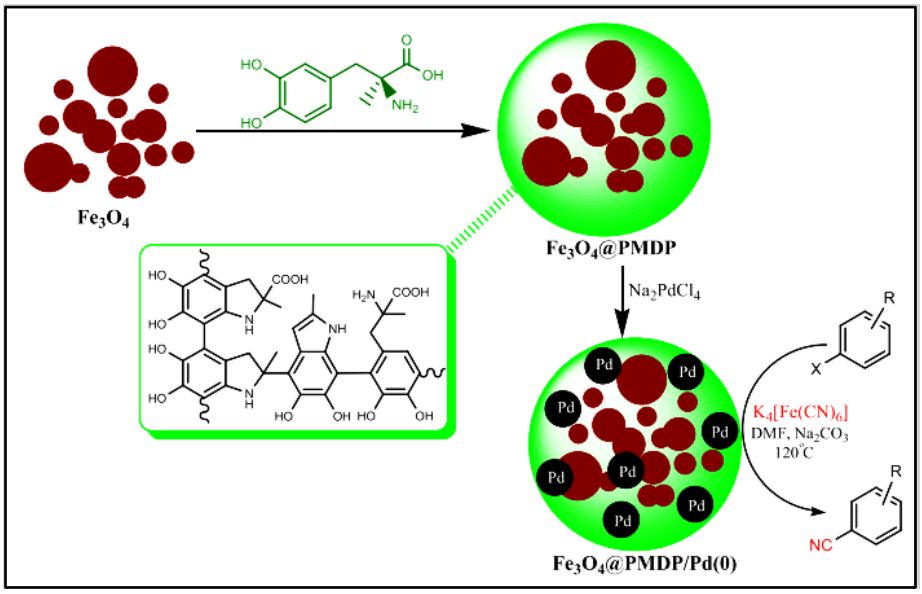
- Active hepatic disease.
- Liver problems as a result of past treatment.
- Hemolytic anemia with direct Coombs positivity.
- MAO inhibitor treatment has a long pharmacological history.
- Pheochromocytoma.
- Hypersensitivity to methyldopa in any form is known.

8. Discussion

8.1 Poly-methyldopa as coating nanoparticles Fe_3O_4 [12]:

Methyldopa with its polymer case as poly-methyldopa has been used as coating nanoparticles Fe_3O_4 (Fe_3O_4@PMDP), this drug was made by using a modest and environmentally friendly process. Hence, utilizing Fe_3O_4@PMDP which acts similarly to a core-shell magnetic coordinator as well as a stabilizer agent, in which Pd nanoparticles are efficiently deposited. Several analytical methods, like energy-dispersive X-ray spectroscopy (EDX), high-resolution transmission electron microscopy (HR-TEM), and field emission scanning electron microscopy (FESEM) (Figure 4), can be used in structure, morphology, and physicochemical characteristics analysis of the produced nanoparticles. Core-shell Fe_3O_4@PMDP/Pd (0) nanoparticles showed superior catalytic efficiency, whereas

Nano catalyst reused for aryl iodides and bromides cyanation with $K_4[Fe(CN)_6]$ (Scheme 2). The generated nitriles are produced in high-to-high yield, the catalyst can be sustained by a recycled process and reused up to 7 times with just a little reduction in catalytic efficiency.



Scheme 2. Fe_3O_4@PMDP/Pd generation and utilization in cyanation of aryl halides via $K_4[Fe(CN)_6$ [12].

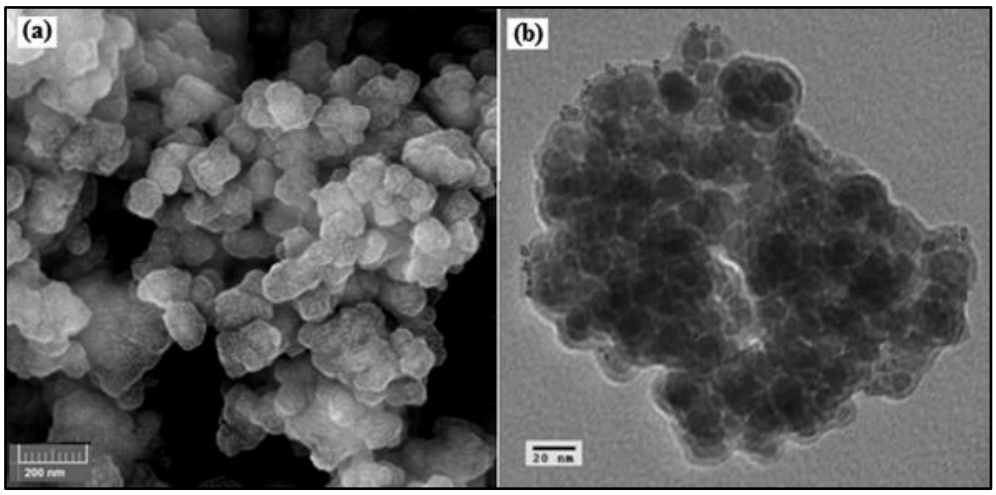


Figure 4. (a) FESEM (b) TEM images of Fe_3O_4@PMDP/Pd [12].

8.2 Methyldopa with Flavonoids as an expression of some factors associated with inflammatory processes or vascular diseases [13]:

The study's goal was to look at the effects of methyldopa and flavonoids (apigenin, baicalein, chrysin, quercetin, and scutellarin) in combination with the in vitro production of certain proinflammatory and vascular indicators to foresee their activity in pregnancy-induced hypertension. The study utilized the trophoblast-derived patient choriocarcinoma cell line as well as a primary patient umbilical vein endothelial cell line. The MTT test was used to assess the cytotoxicity of substances at various concentrations (20, 40, and 100 mol), and the concentration of 40 mol was chosen for future investigation. Following that, their influence somewhat on the expression of certain inflammation-related markers (n (TNF-α; IL-1β; IL-6)) also vascular effects (hypoxia-inducible factor 1α-HIF-1α, placental growth factor–PIGF, transforming growth factor β-TGF-β, vascular endothelial growth factor-VEGF) were investigated somewhere at mRNA and protein levels. Except for PIGF, all examined factors in these cells were downregulated by every flavonoid and methyldopa treatment when combined, particularly where at the mRNA expression level. Because essential hypertension often increases TNF-α, IL-1β, IL-6, HIF-1α, and TGF-β, in addition to VEGF mRNA or protein levels, the outcomes revealed in the investigated model may indicate a good prognosis for the same activity in vivo.

8.3 Methyldopa as a cause of depression [14]:

Studies in epidemiology and pharmacology indicated that methyldopa has a significant role in hormone changes, decreased cerebral blood flow, and reduced neuronal activity that causes postpartum depression and maternal blue. This study demonstrates how critical this issue is to women's health and how complicated its mechanism is.

Methyldopa dramatically raises the vascular endothelial growth factor (VEGF) level, which serves as both a neurotrophin and an angiogenic factor. Owing to such a feature, VEGF reduces serotonin concentration and depletes catecholamines, impairing neurogenesis and affecting the functioning of existing neurons, albeit the change of neurons' functions is likely more complicated. For the neurotrophic hypothesis of depression, these alterations are characteristic.

Methyldopa reduces the sympathetic system's activation and inhibits baroreceptor signaling pathways, which results in a reduction in cerebral blood flow. Lowered cerebral blood flow, particularly in the orbitofrontal cortex, results in depressed mood, reduced cognitive performance, and damaged neuron function. These alterations are distinctive of a vascular depression model (Figure 5).

Methyldopa causes a rise in nitric oxide levels via increasing eNOS expression and decreasing nitric compound outflow in the kidneys. High levels of nitric oxide may cause depression because it is neurotoxic in high concentrations and causes limited inflammation, lower levels of cofactors (such as tetrahydrobiopterin, trytophin, etc.), and reduced levels of serotonin and catecholamines.

In light of the aforementioned, using methyldopa might cause depression. Given that depressed mood and labile affect are prevalent after childbirth and that methyldopa is a first-line therapy for pre-eclampsia as well as gestational hypertension, pregnancy whether pathological or not intensifies this adverse effect of methyldopa.

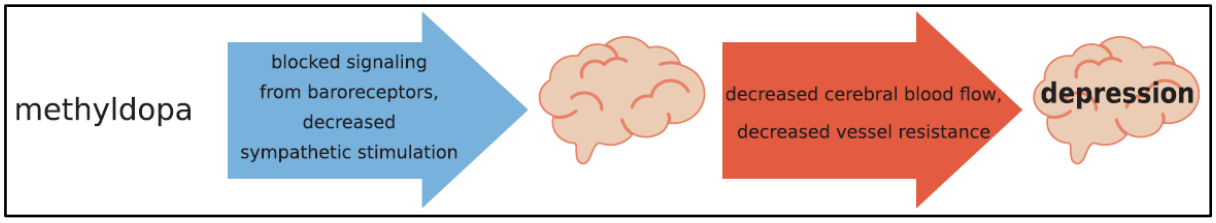


Figure 5. Methyldopa induces depression through a vascular mechanism [14].

9. Conclusions

Improving methods enhanced the role of Methyldopa in the biological field. Where used to regulate and treat hypertension and some industrial application. Thus, Methyldopa is a drug frequently used to control and treat high blood pressure. One of the most often used treatments for high blood pressure during pregnancy is this one. Methyldopa works by relaxing blood vessels further, allowing for easier blood flow throughout the body. Additionally, methyldopa is a medicine that is often taken during pregnancy and is unlikely to endanger the unborn child.

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by Noor E Naoom

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2. Structural Feature of Methyldopa

Methyldopa is a derivative of catechol [3-Hydroxy-α-Methyl-L-Tyrosine]. The chemical formula of methyldopa ($C_{10}H_{13}NO_4$), and its molecular weight (211.21 g/mol), (Figure 1). It is a crystalline powder that can range in color from white to yellowish white or even be colorless. It has no taste or odor and is often dissolved in water [6, 7].

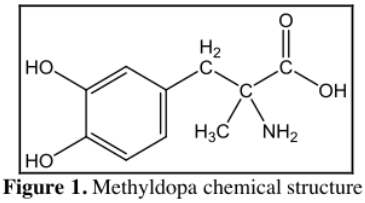

Figure 1. Methyldopa chemical structure.

3. Synthesis of the Drug (Methyldopa)

Methyldopa was manufactured and used a continuous fluidized-bed crystallization resolution racemization method, which, despite being more than 30 years old, remains a great feat in science and technology. Using easily accessible vanillin as a starting point, a simple nitroethane condensation and partial reductive hydrolysis produced methyl vanillyl ketone. The racemic amino nitrile was found by using a typical Strecker reaction (Scheme 1).

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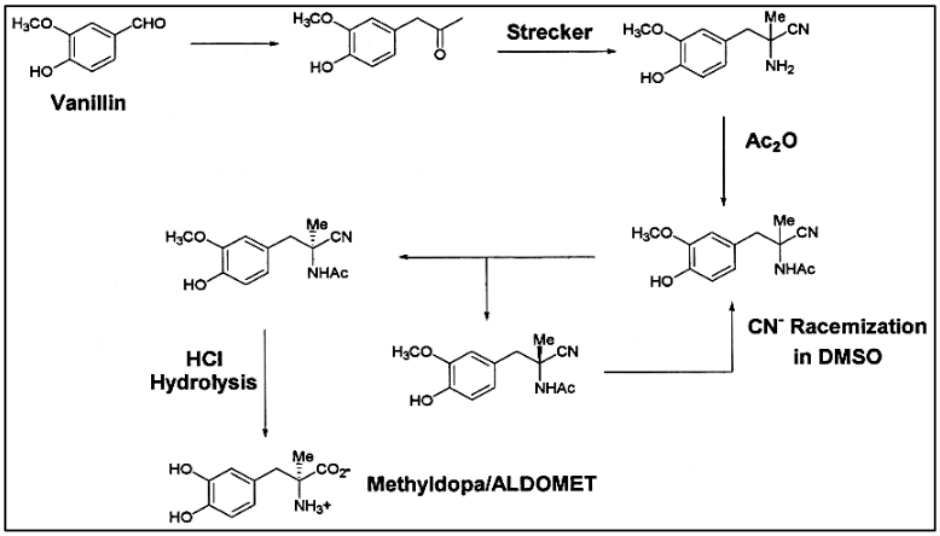

Scheme 1. The manufacturing process of methyldopa [7].

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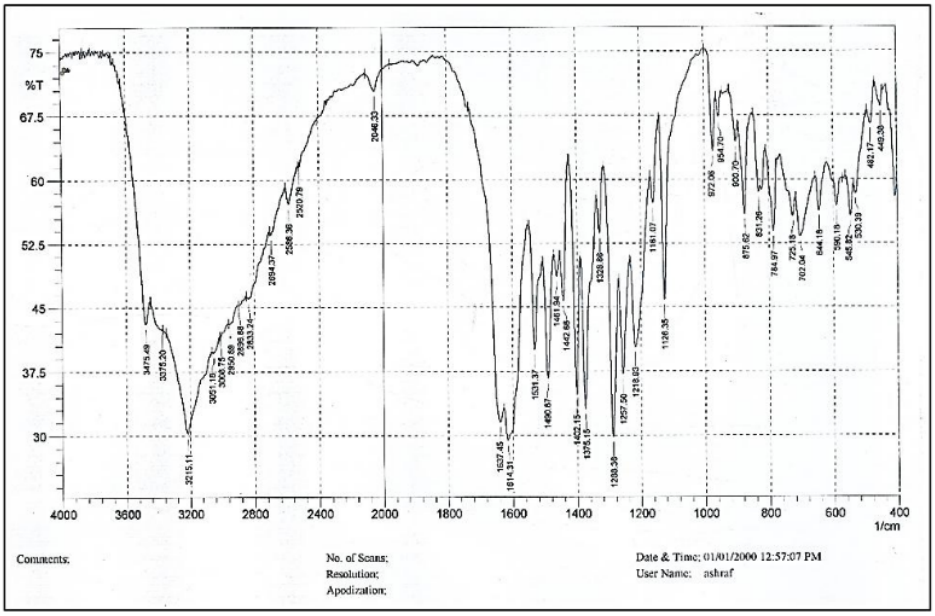
Methyldopa has been characterized by FT-IR spectroscopy device. The FT-IR spectrum showed prominent frequencies at 3475 and 3375 cm^{-1} (for NH_2 stretching vibrations), and 3215 cm^{-1} (for OH stretching vibrations). The ν_{asym} (C=O) of the carboxylic acid group was noticed at 1637 cm^{-1} and ν_{sym} (C=O) 1491 cm^{-1}, 1257 cm^{-1} for (C–N stretching vibration) as illustrated in (Figure 2).



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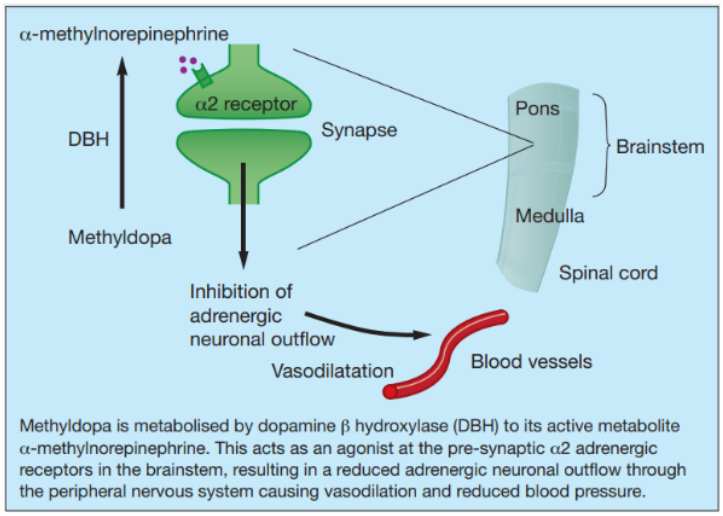

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- Constipation.
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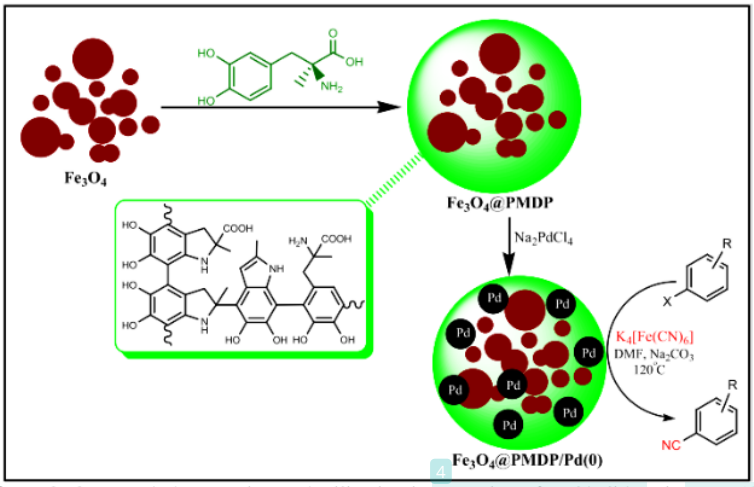
8.1 Poly-methyldopa as coating nanoparticles Fe_3O_4 [12]:

Methyldopa with its polymer case as poly-methyldopa has been used as coating nanoparticles Fe_3O_4 (Fe_3O_4@PMDP), this drug was made by using a modest and environmentally friendly process. Hence, utilizing Fe_3O_4@PMDP which acts similarly to a core-shell magnetic coordinator as well as a stabilizer agent, in which Pd nanoparticles are efficiently deposited. Several analytical methods, like energy-dispersive X-ray spectroscopy (EDX), high-resolution transmission electron microscopy (HR-TEM), and field emission scanning electron microscopy (FESEM) (Figure 4), can be used in structure, morphology, and physicochemical characteristics analysis of the produced nanoparticles. Core-shell Fe_3O_4@PMDP/Pd (0) nanoparticles showed superior catalytic efficiency, whereas

Nano catalyst reused for aryl iodides and bromides cyanation with $K_4[Fe(CN)_6]$ (Scheme 2). The generated nitriles are produced in high-to-high yield, the catalyst can be sustained by a recycled process and reused up to 7 times with just a little reduction in catalytic efficiency.



Scheme 2. Fe_3O_4@PMDP/Pd generation and utilization in cyanation of aryl halides via $K_4[Fe(CN)_6$ [12].

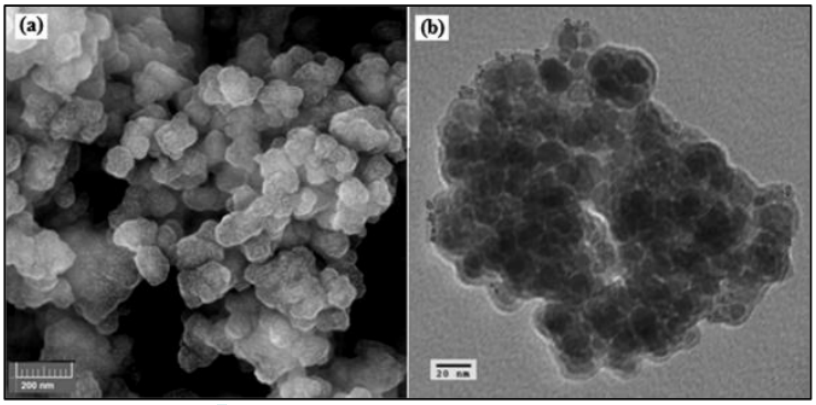


Figure 4. (a) FESEM (b) TEM images of Fe_3O_4@PMDP/Pd [12].

8.2 Methyldopa with Flavonoids as an expression of some factors associated with inflammatory processes or vascular diseases [13]:

The study's goal was to look at the effects of methyldopa and flavonoids (apigenin, baicalein, chrysin, quercetin, and scutellarin) in combination with the in vitro production of certain proinflammatory and vascular indicators to foresee their activity in pregnancy-induced hypertension. The study utilized the trophoblast-derived patient choriocarcinoma cell line as well as a primary patient umbilical vein endothelial cell line. The MTT test was used to assess the cytotoxicity of substances at various concentrations (20, 40, and 100 mol), and the concentration of 40 mol was chosen for future investigation. Following that, their influence somewhat on the expression of certain inflammation-related markers (n (TNF-α; IL-1β; IL-6)) also vascular effects (hypoxia-inducible factor 1α-HIF-1α, placental growth factor–PIGF, transforming growth factor β-TGF-β, vascular endothelial growth factor-VEGF) were investigated somewhere at mRNA and protein levels. Except for PIGF, all examined factors in these cells were downregulated by every flavonoid and methyldopa treatment when combined, particularly where at the mRNA expression level. Because essential hypertension often increases TNF-α, IL-1β, IL-6, HIF-1α, and TGF-β, in addition to VEGF mRNA or protein levels, the outcomes revealed in the investigated model may indicate a good prognosis for the same activity in vivo.

8.3 Methyldopa as a cause of depression [14]:

Studies in epidemiology and pharmacology indicated that methyldopa has a significant role in hormone changes, decreased cerebral blood flow, and reduced neuronal activity that causes postpartum depression and maternal blue. This study demonstrates how critical this issue is to women's health and how complicated its mechanism is.

Methyldopa dramatically raises the vascular endothelial growth factor (VEGF) level, which serves as both a neurotrophin and an angiogenic factor. Owing to such a feature, VEGF reduces serotonin concentration and depletes catecholamines, impairing neurogenesis and affecting the functioning of existing neurons, albeit the change of neurons' functions is likely more complicated. For the neurotrophic hypothesis of depression, these alterations are characteristic.

Methyldopa reduces the sympathetic system's activation and inhibits baroreceptor signaling pathways, which results in a reduction in cerebral blood flow. Lowered cerebral blood flow, particularly in the orbitofrontal cortex, results in depressed mood, reduced cognitive performance, and damaged neuron function. These alterations are distinctive of a vascular depression model (Figure 5).

Methyldopa causes a rise in nitric oxide levels via increasing eNOS expression and decreasing nitric compound outflow in the kidneys. High levels of nitric oxide may cause depression because it is neurotoxic in high concentrations and causes limited inflammation, lower levels of cofactors (such as tetrahydrobiopterin, trytophin, etc.), and reduced levels of serotonin and catecholamines.

In light of the aforementioned, using methyldopa might cause depression. Given that depressed mood and labile affect are prevalent after childbirth and that methyldopa is a first-line therapy for pre-eclampsia as well as gestational hypertension, pregnancy whether pathological or not intensifies this adverse effect of methyldopa.

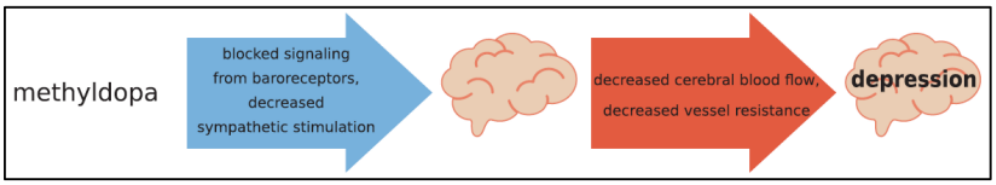


Figure 5. Methyldopa induces depression through a vascular mechanism [14].

9. Conclusions

Improving methods enhanced the role of Methyldopa in the biological field. Where used to regulate and treat hypertension and some industrial application. Thus, Methyldopa is a drug frequently used to control and treat high blood pressure. One of the most often used treatments for high blood pressure during pregnancy is this one. Methyldopa works by relaxing blood vessels further, allowing for easier blood flow throughout the body. Additionally, methyldopa is a medicine that is often taken during pregnancy and is unlikely to endanger the unborn child.

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