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Research Article

Theoretical calculation of some chemical properties of the cannabidiol (CBD) molecule

Şenol Toprak[1]*

[1]Vocational School of Technical Sciences, Amasya University, Amasya/Turkey

Abstract

Lately, many products with the active ingredient cannabidiol (CBD) have been sold around the world. Cannabidiol is an annual herb of the cannabis plant that is known to have no euphoric effects. Another type of terpenophenolic compound known as cannabinoids is also preserved in the structure of the cannabis plant. Products containing CBD are offered on the market as drugs, food supplements or dietary supplements. The US Food and Drug Administration FDA (Food and Drug Administration) has approved the oral solution of Epidiolex (cannabidiol) [CBD] for the treatment of epilepsy in patients aged two years and over. The legal assessment of commercial products containing cannabidiol (CBD) depends on the composition of the drugs available in pharmacies. Depending on whether the drugs also contain tetrahydrocannabinol (THC) in their structure in addition to CBD, criminal narcotics convictions are also decisive. In our study, some parameters related to the chemical structure of the cannabidiol (CBD) molecule were calculated using the Gaussian 09W program and the GaussView 5.0 interface program.

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Cannabidiol,
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1. Introduction

It is believed that cannabinoids have an effect on epilepsy because they act on more than one nerve-to-brain transmission channel and are substances that can influence the receptor mechanism. In addition, studies are being conducted on the versatile biological effects of cannabidiol in various clinical applications, including its antioxidant and anti-inflammatory effects.

[1]Correspondence: senol.toprak@amasya.edu.tr

Research on cannabidiol has increased lately. Under the keyword cannabidiol from 1963 to 2021, the PubMed search found 4107 publications and between 2000 and 2021,3666 publications. First isolated from cannabis in 1940, the structure shown in Figure 1 was not described until 1963 (Mechoulam and Shvo, 1963).

Studies on Cannibas have brought THC (tetrahydrocannabinol), the compound of Cannibas, to the fore. Later scientific studies show that another Cannibas compound, CBD, was ignored. This was undeniably due to the belief that this was due to the psychoactive property revealed by THC rather than CBD. For cannabidiol (CBD), this is unfortunate, as a number of studies on the potential therapeutic benefits of CBD have long been ignored (Burstein, 2015).

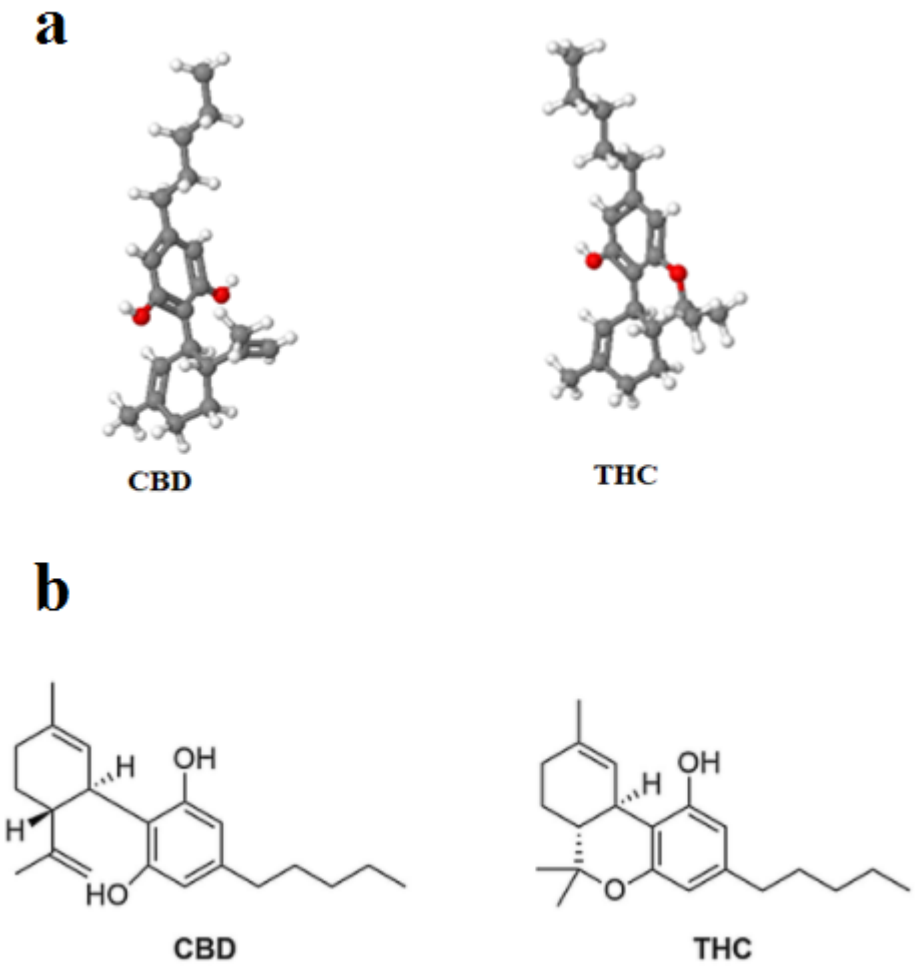

Figure 1. a. The molecular structure and b. chemical diagrams of CBD and D9-tetrahydrocannabinol (THC) (Kosović et al., 2021)

The D9 tetrahydrocannabinol molecule has a highly planar shape in space, while the cannabidiol molecule has a convoluted shape. The difference between these two molecules

when viewed in two dimensions in 1-B results in different pharmacological structures, although there is considerable structural overlap in both molecules.

2. Cannabinoid Receptors and Their Medical Legal Uses

Natural cannabis is found in the structure of the cannabis plant (*Cannabis sativa*) and its effect on cannabinoid receptors known as CB1, CB2 is known in the scientific community (Artuç et al., 2014). In 1964 Gaoni and Mechoulam discovered the chemical components of tetrahydrocannabinol (tetrahydrocannabinol-THC), the main component of the euphoric activity of cannabis (Burstein, 2015). Among the cannabinoid receptors, the CB1 receptor was discovered in 1988 and the CB2 receptor in 1993, and then endocannabinoids (anandamide, 2-arachidonylglycerol) and enzymes that synthesize and break down endocannabinoids (FAAH and MGL) were found (Devane et al., 1988; Munro et al., 1993). After all these studies, interest in the therapeutic use of cannabis has increased and there is an increasing demand for its use in clinical treatments. In 1996 a law was passed in the United States of America that allows the use of medicinal cannabis.

Today, the cannabis license has been legalized in California, Nevada, Massachusetts, and Colorado, as well as in 29 other states in the United States. Recently, many European countries have passed laws on the legal use of cannabis in the medical field. Doctors and scientists also see the legalization of cannabis in the medical field positively. Canada is one of the first countries to conduct legal studies on cannabis liberalization in the medical field and introduced the medical cannabis use license in 2001 (Ulugöl, 2018). In a study carried out in the Canadian state in 2019, it was found that doctors and pharmacists rate the medical use of cannabis positively and, on the basis of personal experience, also cause a lower rate of side effects compared to many treatments (Elias et al., 2019).

3. Components of Cannabis

In addition to the 420 cannabinoids in cannabis, the main active ingredients are the psychoactive compound Δ^9-THC (Figure 1), cannabinol (CBN) (Figure 2), which is less effective (10% percent) than Δ^9-THC, and, the itself Cannabidiol (Figure 1) (CBD) is not a psychoactive substance, which can modify the effects of Δ^9-THC and cannabinol.

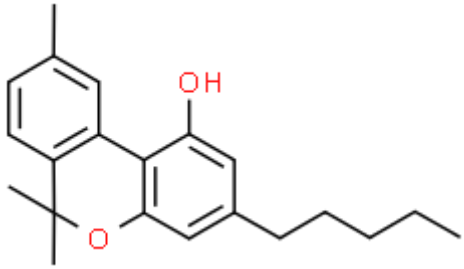

Figure 2. Chemical structure of cannabinol (CNB) (ChemSpider, 2021)

4. Chemical Structure of Cannabinol

The chemical structure of cannabis is extremely complicated, but its structure is well elucidated by today's technology (Lehmann, 1995). The cannabis plant produces different amounts of resin with different concentrations of active ingredients in female inflorescences. Chemical studies on the cannabis plant began in the 19th century. But it was a little late that its structure was finally clarified until 1964 the correct chemical structure of THC was investigated by Gaoni and Mechoulam (Table 1) (Gaoni and Mechoulam, 1964).

Table 1. Chemical and physical data of cannabinol (CBD) molecule (World Health Organization, 2018)

Cannabidiol (CBD)	
CAS:	13956-29-1
Empirical formula:	$C_{21}H_{30}O_2$
Molecular weight:	314.46 g/mol
Melting point	66–67 °C
log P	5.79 (octanol/ water)
Solubilities:	
Water	insoluble
Ethanol	soluble
Chloroform	soluble
Hexane	soluble

Recent research shows that cannabinoids can be counted among the beneficial sources of antioxidants. The CBD structure contains free oxygen atoms. This oxygen atom can bind free radicals and neutralize these radicals. Most likely, this oxygen atom gives CBD its antioxidant activity and can help fight free radicals (Borges et al., 2013).

5. The Medicinal Uses of CBD

Cannabidiol has found the following uses in medicine:

- Epilepsy: especially in certain genetic forms of epilepsy.
- Anxiety Disorders.
- Schizophrenic psychoses.
- Inflammation and pain due to inflammation.
- Movement disorders: dystonia, dyskinesia.
- Substance abuse.
- Nausea and vomiting.

In addition, there is evidence that it can be used in different areas of application, for example in the repair of bones, skin diseases, allergic diseases and the minimization of the inverse effects of the cytostatic agent doxorubicin. Many of these listed properties have hardly been explored for a long time. The effect of cannabidiol (CBD) is based on an antagonism on the CB1 receptor, which binds to the receptor on the vanilloid receptor type 1 (TrpV1).It depends on various effect systems, including the effects it creates.CBD has also been shown to facilitate neurotransmission mediated by the serotonin receptor 5-HT1A (De Gregorio et al., 2019).

6. Materials and Methods

The geometry parameters of the title compound were optimized using the polarized triple zeta split valence 6-311++G (d, p) basis set and the Becke3LYP (Figure 3) functional of density functional theory (DFT). All calculations made in the examination of this molecule were carried out in the Gaussian 09W package program (Frisch et al., 2009). Mulliken Charges and boundary orbitals and boundary orbitals (HOMO-LUMO) distribution and their energy values of CNB levels calculations were performed with the help of GaussView 5.0 imaging program (Roy et al., 2009).

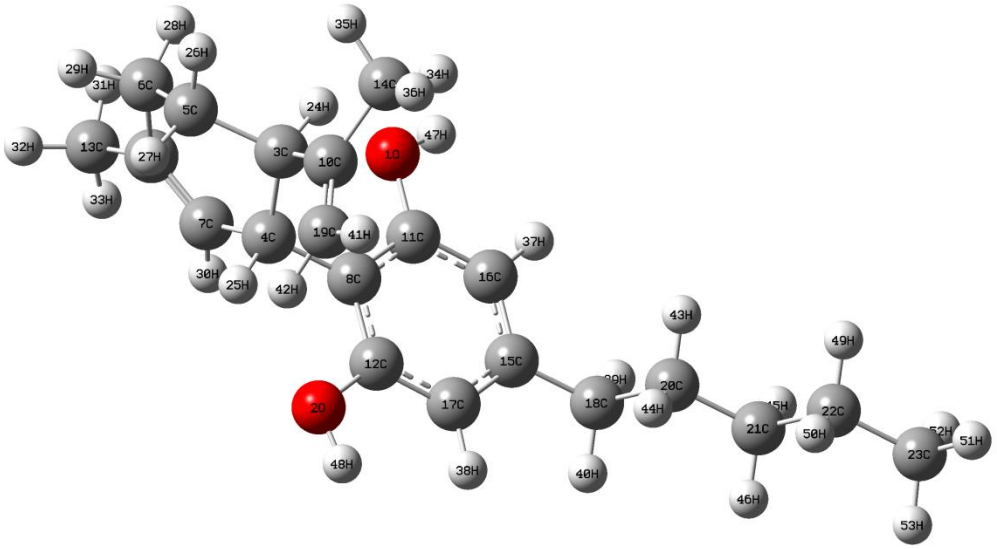

Figure 3. Optimized molecular geometry of cannabinol (CNB) optimized with B3LYP function and the 6–311 + + G (d, p) basis set.

7. Results

The optimized structure, theoretical parameters, boundary molecular orbitals, molecular electrostatic potential value of the title molecule were chosen as the basic set with the help of the DFT method / B3LYP function in the package program Gaussian 09 W and 6-311 + + G (d, p) (Table 2).

Table 2. Calculated bond lengths and angles of cannabinol (CNB) molecule

Parameters	Calculated	Parameters	Calculated
Bond lengths (Å)			
O1-H47	0.962	**C3-H24**	1.093
O2-H48	0.962	**C5-H27**	1.512
C3-C4	1.550	**C5-H26**	1.541
C3-C5	1.545	**C6-H28**	1.532
C5-C6	1.531	**C6-H29**	1.533
C6-C9	1.510	**C13-H31**	1.097
C9-C7	1.335	**C13-H32**	1.096
C7-C4	1.520	**C13-H33**	1.092
C9-C13	1.505	**C14-H34**	1.096
C3-C10	1.522	**C14-H35**	1.096
C10-C14	1.509	**C14-H36**	1.091
C10-C19	1.334	**C19-H41**	1.085
O1-C11	1.372	**C19-H42**	1.083
O2-C12	1.373	**C17-H38**	1.087
C8-C11	1.403	**C18-H39**	1.095
C8-H12	1.403	**C18-H40**	1.095
C12-C17	1.396	**C20-H43**	1.096
C17-C15	1.393	**C20-H44**	1.096
C15-C16	1.394	**C21-H45**	1.098
C16-C11	1.396	**C21-H46**	1.098
C4-C8	1.525	**C23-H53**	1.094
C15-C18	1.512	**C23-H51**	1.093
C18-C20	1.541	**C23-H52**	1.095
C20-C21	1.532	**C22-H49**	1.096
C21-C22	1.533	**C22-H50**	1.096
C22-C23	1.531	**C4-C25**	1.093
C7-H30	1.087		
Bond angles (^{0})			
C5-C6-C9	112.7	**C11-C16-C15**	120.7
C6-C9-C7	121.3	**C16-C15-C17**	118.1
C9-C7-C4	125.4	**C15-C17-C12**	120.5
C7-C4-C3	111.3	**C17-C12-C8**	122.4
C7-C4-C8	111.1	**C21-C22-C23**	113.2
C4-C8-C11	123.1	**H38-C17-C15**	119.9
C4-C3-C10	115.3	**H38-C17-C12**	119.4
O1-C11-C8	117.4	**O1-C11-C16**	120.2
H47-O1-C11	109.1	**O2-C12-C8**	117.3
H48-O2-C12	109.2	**O2-C12-C17**	120.2
C8-C11-C16	122.2	**H43-C20-H44**	106.0

7.1. HOMO-LUMO Analysis

The energy levels of a neutral cannabinol (CNB) molecule, the highest occupied molecular orbital (HOMO), and the lowest unoccupied molecular orbital (LUMO), play an important role in maintaining the properties of molecular structures.

From the HOMO-LUMO energy data and diagrams, we can obtain information about the chemical activity and the kinetic stability of the CNB molecule under study. HOMO is in electron donating orientation, LUMO is in electron accepting orientation and these orbitals can be used to calculate charge transfer. Here, the HOMOs and LUMOs diagrams and energy values of the CNB molecule are given in Figure 4 and calculated parameters in Table 3.

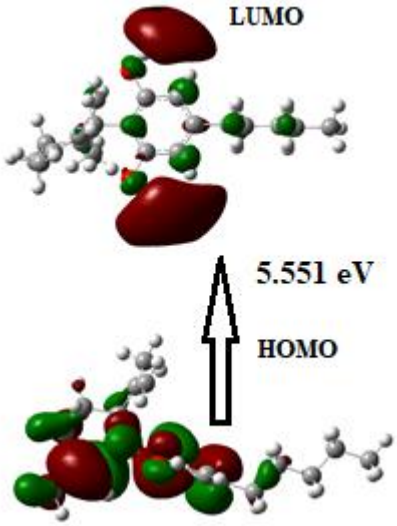

Figure 4. For cannabinol (CNB) according to the B3LYP / 6-311 ++ G (d, p) method, difference between calculated ΔE (E_{HOMO}-E_{LUMO})

Table 3. Calculated parameters of cannabinol (CBD)

Parameters	**Method** [B3LYP / 6-311 ++ G (d, p)]
E_{HOMO} (eV)	-6.027
E_{LUMO} (eV)	-0.476
ΔE (eV)	5.551
Dipol Moment (Debye)	2.5792
Energy of CBD (kcal/mol)	$-6.080 \cdot 10^5$

The DFT calculation approach shows that HOMO and LUMO for the compound examined correspond to the π and π * orbitals of the benzene ring (Figure 1). Due to their delocalization, these orbitals are mostly distributed over the adjacent double bond areas of the compound. Every HOMO energy calculation of the compound is consistent with previous publications (Kumer et al., 2019).

7.2. Molecular Electrostatic Potential (MEP)

The molecular electrostatic potential (MEP) can be defined as the interaction energy of the positive test charge and the charge distribution in the molecular system. The color coding system is used to interpret the molecular electrostatic potential. On the MEP map, the most negative potential (the area in which the entire surface of the molecule is electron-dense compared to the nucleus) is colored red, while the positive potential (the area in which partial positive charges are concentrated) is shown in blue (Cramer, 2004). The intermolecular interaction plays a key role in MEP, where the positions of the molecules are close together. Where a molecule is most negative on the MEP map indicates areas most susceptible to electrophilic attack (Levine, 2000). The MEP map of cannabidiol (CBD molecule is shown in Figure 5). The negative region of the molecule resides on the carbon atoms on the phenolic ring and on the oxygen atoms on the phenolic ring, while these areas are considered the most suitable areas for electrophilic attack. The arrangement of the positive areas can be seen around the methyl groups and hydrogen atoms (Figure 5).

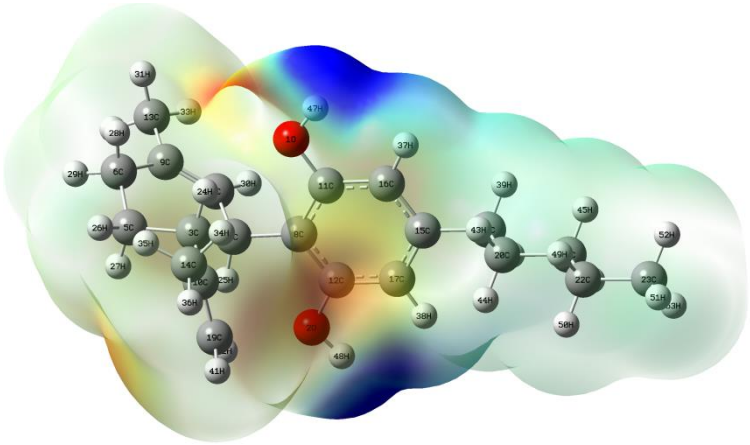

Figure 5. Molecular electrostatic potential (MEP) surface of the cannabidiol (CBD) molecule

7.3. Mulliken Atomic Charges of Cannabinol (CBD)

Molecular structures are an important parameter in the application area of calculations based on quantum chemical methods. While the charge transfer occurs via the distribution of the atomic charges, we can obtain information about the dipole moment and the electronic configuration of the molecular structure in the donor and acceptor areas of the molecule.

The Mulliken charge distributions of the molecule were calculated in the gas phase using the DFT / B3LYP / 6-31 ++ G (d, p) method (Table 4).

Table 4. Mulliken Atomic Charges of Cannabinol (CBD)

Atoms	Mulliken Charge	Atoms	Mulliken Charge
O1	-0.16	C13	-0.47
O2	-0.19	C14	-0.61
C3	-0.01	C15	0.96
C4	0.82	C16	-0.72
C5	-0.27	C17	-0.61
C6	-0.84	C18	-0.28
C7	-0.34	C19	-0.84
C8	0.61	C20	-0.32
C9	0.03	C21	-0.24
C10	0.39	C22	-0.16
C11	-0.32	C23	-0.64
C12	-0.48	H24	0.22

If you look at Table 4, when you look at the given charge distributions, you can see that the electronegativity of the negative charges from the gas phase is mainly concentrated on the carbon atoms on the benzene ring and on the O1 and O2 oxygen atoms, which are also bound to the benzene ring. The different values of the charge distribution between the atoms are an indicator of the polarization of the molecule.

7.4. Theoretical Raman Spectrum of Cannabinol (CBD)

The data of the vibrational movements corresponding to the peak points obtained from the simulations of the Raman spectra for the cannabidiol (CBD) molecule were carried out with the analysis program GaussView, which can calculate the Raman spectra. A simulated spectrum was obtained from the Raman frequencies calculated by this program, and it was possible to predict the vibrational motions representing each Raman peak. In addition, randomly selected peaks and various publications that may give characteristic frequencies of the molecule under study were examined to confirm the accuracy of the GaussView program. Table 5 shows the characteristic frequencies selected for the cannabidiol (CBD) molecule.

Table 5. Characteristic Raman frequencies of the calculated Cannabinol (CBD) molecule

Molecular Vibration	Raman Shift(cm-1)
Benzene Breathing/ C-C Stretch	1624.5
C=C Stretch (ring)	1655.45
C=C Stretch (alkene)	1704.0
O-H Stretch	3836.04, 3841.93
C-H Deformation	3065.3, 3037.09, 3129.79

4. Conclusion

With the B3LYP function and the 6–311 + + G (d, p) basis set, quantum chemical calculations of the calculation results of the optimized structure, such as boundary molecular orbitals, molecular electrostatic potential and nonlinear properties, were carried out (Figure 6).

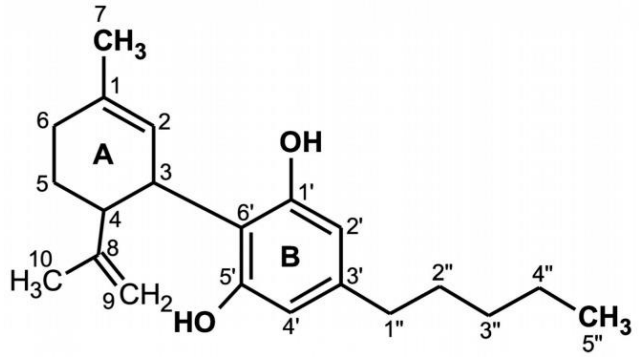

Figure 6. Numbered atoms of the cannabidiol (CBD) molecule (Atalay et.al, 2020).

Cannabinol (CNB) molecule has two rings as phenol and cyclohexene (Figure 5). The chemical activity of cannabinol (CNB) can generally be due to the attachment of hydroxyl groups to the C-1 'and C-5' atoms of the phenolic B ring and similarly the methyl group to the C-1 atom of cyclohexene-A-Ring. The attachment of the pentyl chain to the C-3 'atom of the B ring can also contribute to the reaction activity of the molecule under consideration. However, the cyclohexene ring in the Cannabinol (CNB) molecule is inactive because it is an open ring from the position of the C-4 atom. Due to the presence of hydroxyl groups attached to the C-1′ and C-5′ atoms in the B ring of the cannabinol (CNB) molecule, it can bind to amino acids such as threonine, tyrosine, glutamic acid or glutamine via a hydrogen bond (Elmes et al., 2015).

Table 6. Comparison of Raman frequencies of Cannabinol (CNB) molecule from different calculated studies

Vibrational Motion	[a]Raman Shift (**cm^{-1}**) CBD	Raman Shift (**cm^{-1}**) CBD
Benzene Breathing /C-C Stretch	1605.8	1624.5
C=C Stretch	1674.2	1655.45
O-H Stretch	3719.4, 3724.5	3836.04, 3841.93
C-H Deformation	2921.2, 3038.5, 3119.4	3065.3, 3037.09, 3129.79

[a](Sigworth, 2020)

The C = C stretch for CBD at 1655.45 cm^{-1} is consistent with previous studies. It is important to determine the characteristic frequencies for CBD with Raman and to compare Raman data from the analysis of other cannabinoids.

The cannabidiol molecule is a difficult molecule to optimize because an alkene is very close to the phenol in its structure. Many optimization attempts either fail or lead to the removal of a phenol group from the cannabidiol molecule, which leads to a free water molecule, which also leads to the destruction of the terminal alkene. Optimizing the molecule resulted in an extremely strong repulsion between the terpene ring and both phenolic groups of CBD, as confirmed in previous studies. There are fewer resources for characterizing CBD vibrational modes. However, although many of the modes have been explored for the D-9 THC molecule, these modes agree well with the modes characterized for the CBD molecule. The GaussView program was used to calculate these modes (Sigworth, 2020).

Some Raman vibration values for the CBD Molecule in Table 6, it is compared to another study of this molecule in the literature. Although there are few studies on this molecule, this is a downside to publication because it is a not fully explored molecule, there is a large area of study for scientists.

References

Artuç, S., Doğan, K. H., Demirci, Ş. 2014. Uyuşturucu maddelerde yeni trend sentetik kannabinoidler, Adli Tıp Bülteni, 19(3): 198-205.

Atalay, S., Jarocka-Karpowicz, I., Skrzydlewska, E. 2020. Antioxidative and anti-inflammatory properties of cannabidiol, Antioxidants, 9(21): 1-20.

Borges, R. S., Batista, J., Viana, R. B., Baetas, A. C., Orestes, E. et. al. 2013. Understanding the molecular aspects of tetrahydrocannabinol and cannabidiol as antioxidants, Molecules, 18(10): 12663-12674.

Burstein, S. 2015. Cannabidiol (CBD) and its analogs: a review of their effects on inflammation, Bioorganic and Medicinal Chemistry, 23(7): 1377-1385.

ChemSpider, An Online Chemical Information Resource, http:// www. chemspider. com/ Chemical-Structure, (August 2021).

Cramer, C. J. 2004. Essentials of computational chemistry: theories and models, computational chemistry. John Wiley & Sons Ltd, England.

De Gregorio, D., McLaughlin, R. J., Posa, L., Ochoa-Sanchez, R., Enns, J. et. al. 2019. Cannabidiol modulates serotonergic transmission and reverses both allodynia and anxiety-like behavior in a model of neuropathic pain, Pain, 160: 136-150.

Devane, W. A., Dysarz, F., Johnson, M. R., Melvin, L. S., Howlett, A. C. 1988. Determination and characterization of a cannabinoid receptor in rat brain, Molecular Pharmacology, 34(5): 605-613.

Elias, R., Raheb, M., Istasy, M., Mekhaiel, D., Sidhu, G., et. al. 2019. Knowledge of cannabinoids among patients, physicians, and pharmacists, Archives of Psychiatry and Behavioral Sciences, 2(1): 25-28.

Elmes, M. W., Kaczocha, M., Berger, W. T., Leung, K., Ralph, B. P., et. al. 2015. Fatty acid-binding proteins (FABPs) are intracellular carriers for Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD), Journal of Biological Chemistry, 290(14): 8711-8721.

Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A. et. al. 2009. GAUSSIAN 09. Revision D. 01. Gaussian Inc. Wallingford. CT, USA.

Gaoni, Y., Mechoulam, R. 1964. Isolation, structure, and partial synthesis of an active constituent of hashish, Journal of the American Chemical Society, 86(8): 1646-1647.

Kosović, E., Sýkora, D., Kuchař, M. 2021. Stability study of cannabidiol in the form of solid powder and sunflower oil solution, Pharmaceutics, 13(412): 1-10.

Kumer, A., Sarker, N., Paul, S., and Zannat, A. 2019. The theoretical prediction of thermophysical properties, HOMO, LUMO, QSAR and biological indics of cannabinoids (CBD) and tetrahhdrocannabinol (THC) by computational chemistry, Advanced Journal of Chemistry-Section A, 2(3): 190-202.

Lehmann, T. 1995. Chemische profilierung von *Cannabis sativa* L. [Chemical profile of *Cannabis sativa* L.]. PhD Thesis. Pharmazeutisches Institut Universität Bern.

Levine, I. N. 2000. Many-electron atoms. Quantum chemistry. Prentice- Hall Inc, New Jersey.

Mechoulam, R., Shvo, Y. 1963. Hashish—I: the structure of cannabidiol. Tetrahedron, 19(12): 2073-2078.

Munro, S., Thomas, K. L., Abu-Shaar, M. 1993. Molecular characterization of a peripheral receptor for cannabinoids, Nature, 365(6441): 61-65.

Roy, D., Todd, K., John, M. 2009. Gauss View; Version 5; Semichem. Inc.: Shawnee Mission, KS, USA.

Sigworth, K. 2020. Raman spectroscopy study of delta-9-tetrahydrocannabinol and cannabidiol and their hydrogen-bonding activities. Honors Theses. University of Mississippi, USA.

Ulugöl, A. 2018. Kannabis bitkisi ve kannabinoidlere giriş. Turkiye Klinikleri Pharmacology-Special Topics, 6(1): 1-5.
United Nations Office on Drugs, and Crime. 2009. Recommended methods for the identification and analysis of cannabis and cannabis products: Manual for use by national drug testing laboratories. United Nations Publications,
https://www. unodc.org/ documents/ scientific/ST-NAR-40-Ebook_1.pdf, (August, 2021).