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Bioactive Compounds of Hemp (*Cannabis sativa L.*): A Review of Their Potential Therapeutic Applications

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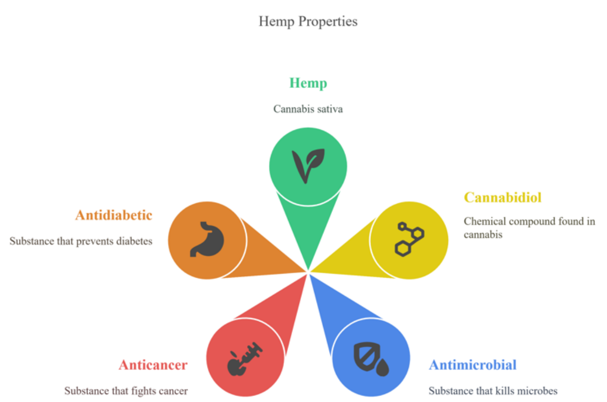
Graphical abstract



Abstract

Hemp (*Cannabis sativa* L.) is a medicinally important species that grows worldwide in a wide range of climatic conditions. Hemp contains various bioactive compounds/phytochemicals such as terpenes, flavonoids, fatty acids, and sterols, which enhance its pharmacological properties. Hemp-based medicine has been found effective against post-traumatic stress disorder, cancer, AIDS, sclerosis, anxiety, depression, inflammation, epilepsy, Tourette syndrome, and sleep disorders. In the current review of literature, approximately 100 bioactive chemicals were identified from research papers that have been published. All recovered compounds were assessed independently for their toxicity, and 22 of them were found to be exceptionally bioactive and had no harmful effects. Furthermore, this overview of literature will reveal LD_{50} values for the extremely bioactive compound, which could potentially be implemented later on as potential therapeutic agents against cancer receptor proteins, cardiovascular disease, antidiabetic, respiratory diseases, and gastro-intestinal problems through an in-silico approach. The present review aims to explore the hemp bioactive metabolites which serve as a potential candidate for treating number of serious diseases.

Keywords: Hemp (*Cannabis sativa* L.); Cannabidiol (CBD); Antimicrobial; Anticancer; Antidiabetic.

1. Introduction

Hemp (*Cannabis sativa* L.) is an herbaceous plant belonging to the family Cannabaceae, commonly cultivated across temperate regions of the northern hemisphere (Palmieri *et al*. 2021). Wild hemp is native to Central and Southeast Asia, but is grown widely across Pakistan – including Khyber Pakhtunkhwa (KPK), Punjab, Sindh, Baluchistan, and the federal areas, as well as in Southern Caspian area, Siberia, China, India, and the Himalayas (Merlin 2003; Younas *et al*. 2024). *Cannabis sativa* L. is hardy, fast growing crop characterized by a broad leaf canopy, which enables it to produce high yields without relying on fertilizers or chemical pesticides (Shams *et al.* 2020). Its extensive root system improves soil aeration, moisture retention, and nutrient cycling, providing a favourable microenvironment for surrounding organisms. Furthermore, hemp exhibits remarkable drought-tolerance, making it a promising candidates for developing water-efficient and climate resilient crops (Gill *et al.* 2022). Across cultures and regions, Cannabis is known by a multitude of vernacular names and synonyms, including ganja, hashish, marijuana, pot, weed, bhang, and sinsemilla, along with regional strains names such as Acapulco Gold, Panama Red, and Thai Stick (Hourfane *et al.* 2023). Other colloquial terms include dope, reefer, joint, spliff and doobie. Over time, the term "Sativa" and "Indica" have evolved into informal medical classification, often replacing common botanical nomenclature. Sativa-dominant varieties are associated with energizing and stimulating properties, used to alleviate depression, headaches, nausea, and appetite loss, whereas Indica strain produce relaxing and sedative effects, commonly applied in management of insomnia, pain, inflammation, muscle spasms, epilepsy, and glaucoma (Black and Capler 2003; McPartland and Guy 2017). The phytochemical content of two subspecies (sativa and indica) differs significantly: *Cannabis sativa* generally contains less than 0.3% THC by weight, whereas *Cannabis indica* exceeds this threshold, resulting in psychoactive effects. Conversely, *C. indica* has lowered cannabidiol (CBD) compared to *C. sativa* (Bukowska 2024).

Plants, including Cannabis, synthesize a wide array of pharmacologically active compounds, many of which serve as the basis for modern pharmaceuticals (Dehelean *et al.* 2021). Historical records suggest that hemp has been used by humans for fibers, food, and medicinal purposes for over 5000 years (Appendino *et al*. 2014). According to Shams et al. (2020), hemp (*Cannabis sativa* L.) contains more than 600 distinct chemical compounds, comprising both primary metabolites (e.g., amino acids, fatty acids, and steroids) and secondary metabolites (e.g., terpenoids, flavonoids, cannabinoids, stilbenoids and lignans). These compound exhibits remarkable health-promoting and therapeutic potential (Shujat *et al.* 2022). Phytochemicals are mainly concentered in glandular trichomes of female flowers, whereas cannabinoids (CBD) and terpenoids are biosynthesized (Jin *et al.* 2020; Dimopoulos *et al.* 2025). To date, 113 cannabinoids have been identified, with Δ^9-tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabigerol (CBG) recognized as the most biologically active. Their acidic precursors, THCA and CBDA are present in plants, but decarboxylate into their active forms upon exposure to heat or light (Kotiranta *et al.* 2024). Among other phytochemical, terpenes constitute the second largest group, primarily consisting of sesquiterpenes and monoterpenes, which contribute to plant’s aroma and bioactivity.

Historically, hemp has been cultivated for industrial applications such as the production of ropes, textiles, paper and sails (Karche 2019). In recent decades, its bioactive compounds have gain attention for potential use in pharmaceuticals, nutraceuticals, food additives, drugs, fragrances, and biopesticides (Trono 2024). Nutritionally, hemp seeds are rich in proteins, essential fatty acids, minerals, and antioxidants making them a valuable dietary source. The crops serve multiple industrial purposes, including construction materials, shelter insulation, animal feed, human nutrition, bioplastics, and biocomposites (Ahmed *et al.* 2022; AL Ubeed *et al.* 2022). Additionally, hemp derivatives are also utilized in cosmetic, such as hair serum made from seed powder (El Khomsi *et al.* 2022) and in food products including gluten-free flour, pasta and beer. Moreover, hemp proteins show promising potential in environmental remediation – for example, effectively chelating polyfluoroalkyl substances (PFAS) in contaminated groundwater (Turner *et al.* 2019), and ameliorating salt-effected (Cosarca *et al.* 2017).

Cancer of colon is among the most prevalent and lethal tumors globally due to limited early diagnosis and treatments. Cannabis interacts with the intestinal ECS through CB1 and CB2 receptors, other G-protein-coupled receptors, endogenous ligands, and enzymes that degrades the compounds (Grill *et al.* 2018). There are various mechanisms through which *Cannabis sativa* inhibits proliferation, inflammation, apoptosis and angiogenesis in CRC (Silva-Reis *et al.* 2023). Despite this, little research has been done on using bioactive substances of *C. sativa* for the treatment of this cancer. This present review aims to provide a comprehensive overview of bioactive compounds of hemp (*Cannabis sativa* L.) and their potential therapeutic applications. Furthermore, it emphasizes a systematic screening framework, that integrates computational and experimental approaches to accelerates the identification, validation, and development of potent hemp-based therapeutics candidates.

2. Plant Characteristics and Growth Condition

Hemp (*Cannabis sativa* L.) can grow in a wide range of environments due to its high adaptability. It prefers a mild climate with temperatures between 15 to 27 °C and does not tolerate frost. It needs consistent moisture during the seedling stage and rainfall between 600 and 1200 mm (Small 2017). It is referred to as heliophyte and requires ample exposure to direct sunlight during its vegetative stage. The life cycle of a plant has four stages: 1) Seedling, 2) Vegetative, 3) Flowering and Seedling, and 4) Senescence (Hesami *et al*. 2023). Plant can achieve a height of 2-4 meters. Normally, plants are dioecious, herbaceous, and shrubby in nature with fluted stems. The plant leaves are stipulated, opposite, palmate, and serrated, with most with primary serration and few with secondary serration (Dalli *et al*. 2023). Near the top of the plant, the leaves become alternating, simple, hairy, and simply three-segmented. Female plants have bunchy leaves; thus, they can be distinguished easily from male plants by their spindlier appearance. They have tectorial, cystolithic, and resin-secreting hairs (Dalli *et al*. 2023). Small glandular hairs cover the tiny leaves beneath the flower clusters and form a network-like surface on the bracts. Flowers cluster loosely, and leaves are stalkless. The seeds have a net-like pattern between irregular dark spots, along with a raised base (McPartland and Guy 2017). Male and female plants are not distinguishable during early growth. Sexual dimorphism is only visible during the last growth phase, when flowers are formed (Schilling *et al.* 2020). The flowers in female are apetalous and have two elongated stigmas, which can be white, yellow or pink. A diminutive calyx (<3.6 mm) covers the ovary, which bears a solitary ovule (Lynch *et al.* 2016). Male flowers have five sepals are about 5 mm in length, often yellow, while and greenish colored. The male plants produce pollen sacs that shed pollen to pollinate the receptive, resinous female stigmas (Anwar *et al.* 2006). The seeds are smooth, greyish ovoid or spherical, measuring 2.5 to 4.0 mm long and 2.5 to 3.5 mm in diameter. Each seeds contains two cotyledons that are rich in protein and oil, with a notably small albumen compared to other plant species (Bouloc 2006). Essential oils containing CBD content ranging from 6.9 percent to 52.4% have been observed (Zheljazkov *et al*. 2020). It has been demonstrated that light cycles and environmental factors play a key role in regulating flowering genes across different plant families, from germination to senescence (Ahsan *et al*. 2024).

3. Hemp Bioactive Compounds and Their Pharmacological Properties

Hemp (*Cannabis sativa* L.) is abundant in bioactive compounds and a promising potential candidate for treating many diseases. Fiber, food, and medicine can all be derived from hemp. Over 600 bioactive compounds present in hemp belongs to specific compounds class including phytocannabinoids, terpenoids, stilbenoids, fatty acids, lignanamides, flavonoids, steroids, sugars and alkanes **(Figure 1)** reported by (Solymosi and Kofalvi 2017; Hourfane *et al.* 2023). Phytocannabinoids is 21-C compounds having benzopyrene group and resorcinol side chain in structure breakdown original compounds into products such as cannabinol type (CBN), cannabigerol, cannabidiol (CBD), cannabitriol, cannabichromen, tetrahydrocannabinol (THC), and cannabidiolic acid (Stasilowicz *et al*. 2021). Bioactive compounds in hemp reportedly stimulate the human and animal endocannabinoid system, which controls physiological and cognitive processes (mood, appetite, memory, and immune response). Previous finding of Schilling *et al*., (2020) described that human nerve cells are covered with endocannabinoid receptors, and Cannabis' phytocannabinoids bind to these receptors. Cannabis-based medicine has been found effective against post-traumatic stress disorder, cancer, AIDS, sclerosis, anxiety, depression, inflammation, epilepsy, Tourette syndrome, and sleep disorders (**Table 1**). Chen and Pan, (2021) reported that CBD is a key metabolite of hemp, has been gaining a lot of attention due to its pharmacological properties, such as pain relieving, anti-emetics, antipsychotics, and immune-suppressants. Different cultures applied *Cannabis sativa* for distinct purposes. In China, it was used to treat conditions like fatigue, malaria, and rheumatism, with the seeds serving as a protein source. Conversely, Egyptian women utilized the plants for its analgesic and mood-elevating properties (Ovatlarnporn *et al.* 2025; Malabadi *et al.* 2023). As reported in Andre *et al*., (2016), CBD concentration varies between hemp strains, ranging from 1790 μg/g (leaves) to 8590 μg/g (flower) in wild hemp (*Cannabis sativa*). Genetics may affect cannabinoids, but plant type, age, nutrition, humidity, light levels, harvest time, and storage conditions also have strong influences. Researchers have established that seeds lack cannabinoids (CBD) while roots and pollen contain modest amounts (Trono 2024).

Earlier research has postulated that the nutraceutical quality of *Cannabis sativa* is associated with its high content of bioactive substances. This is reflected in research work of Lowe *et al.* (2021), who elaborated on the occurrence of 120 terpenoids classified as 61 monoterpenoids, 52 sesquiterpenoids, and 7 triterpenoids along with 26 flavonoids and 20 steroids. Researchers have identified that these terpenes in hemp that are capable of fighting cancer, gastroesophageal reflux disease, diabetes, rheumatoid arthritis, antimicrobial and viral infections as shown in **Figure 1** (Singh and Sharma 2015). It is believed that monoterpenes are made up of α-pinene, D-limonene, β-myrcene, and terpinolene while the later group found to be bitter tasting contains caryophyllene, humulene, and caryophyllene oxide (Happyana and Kayser 2016). Hemp inflorescence contained 1.2 to 2.4% or (3.1 to 28.3 mg/g) terpenes by dry weight (Izzo *et al.* 2020). Phenol and flavonoids naturally occurring antioxidant compounds that can neutralize reactive oxygen species (ROS) and prevent them from causing cellular damage. Under stress conditions, they can upregulate enzyme activities such as SOD, CAT, GPX, POD that can eliminate oxidative damage. These compounds have antiaging, neuroprotective and cardioprotective properties (Albuquerque *et al*. 2021). A study estimated that hemp inflorescence contained 80% flavonoids and 20% phenolic compounds, respectively. It was determined that the flavonoid content was 455 mg/kg and the phenolic content was 123.6 mg/kg dry weight, respectively (Izzo *et al*. 2020). The finding of Kotiranta *et al*. (2024) demonstrated presence of more than 20 flavonoids compounds in hemp, such as cannflavin A, cannflavin B, and cannflavin C are prenylated flavonoids (Kotiranta *et al*. 2024). Flavones and flavonol are two types of flavonoids that include vitexin, orientin, quercetin, luteolin, apigenin, and kaempferol. Flavonoids are highest in leaves, followed by inflorescences, and not found in stem barks or roots (Jin *et al*. 2020). Stilbenes are phenolic derivatives which appear in the largest concentrations in the foliage, flowers, and stem, whilst seeds are exceptionally high in lignans (amides and lignanamides) suggested by Padilla-Ganzalez *et al*., (2023).

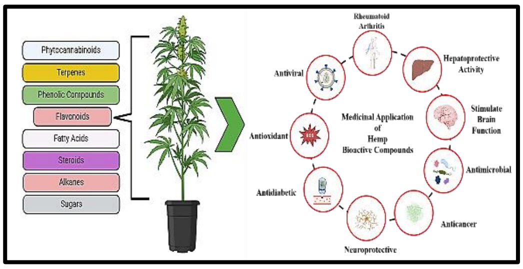


Figure 1: Phytoactive metabolites to major compound class in hemp and their pharmacological properties.

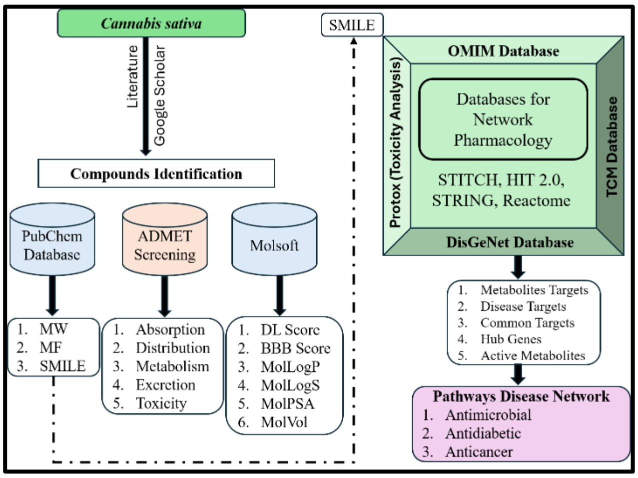


Figure 2. Databases for data mining, screening of bioactive compounds derived from medicinal plants, target predictions and construction of pathways associated for different diseases.

Table 1. Bioactive compounds in hemp inhibit a key receptors molecule against several diseases.

Bioactive Compounds	Potential Target (Receptor Protein)	Key Enzymes	Disease Activity	References
Oleoyl ethanolamide, Palmitoylethanolamide, Arachidonic acid	Type 1 Vanilloid Receptor (TRPV1), Proliferator-activated Receptor (PPAR)	Fatty acid amide hydrolase (FAAH), Monoacylglycerol lipase	Anti-inflammatory Activity	Vuckovic *et al*. 2018
Cannabidiol (CBD)	CB1, CB2	FAAH	Immunosuppressive	
Effect	Boggs *et al*. 2018			
THC, Galantamine, Rivastigmine, Cannibidiorcol, Donepezil	Protein receptor IDs (4PQE, 6IYC, 1SZG, 4BDS)	AChE, Gamma-secretase, BACE1, BuChE	Anti-Alzheimer's agent	Patil *et al.* (2023)
Ambrosin, Tussilagonone, Malyngamide, Diosmetin, CBD, Licoagroaurone, and Tocopheronic acid	Amylase (PDB ID: 6TOZ) and glucosidase (PDB ID: 5ZCB)	Phosphoinositide 3-kinase/Protein Kinase B	Antidiabetic activity	Ovatlarnporn *et al.* (2025)
THC, α-humulene, β-caryophyllene	Receptors proteins IDs (4ITY & 3KV2)	Leishmania mexicana arginase (LmArg) & human arginase (h-Arg)	Anti-Leishmania activity	Assouab *et al.* (2022)
THC, CBD	ACE2, Protease, Papain like protease	---	Antiviral Activity (SARS-CoV-1 & SARS-CoV-2)	Altyar *et al*. 2022
THC, CBD, CBG, cannflavin A, Terpenes	p21, p27	Akt kinase	Anticancer Activity	Farhan *et al*. 2017
Anilionpyrimidines	CDK9 (PDB: 4BCJ)	Cyclin-dependent kinase	Anticancer Activity	Eskandrani *et al*. 2023
Benzenemethanaminium, Dronabinol, Cannabielsion, Squalene	C-reactive protein, TNF- α, IL6	---	Anti-inflammatory Activity, Diabetic Cardiomyopathy	Chauhan *et al*. 2024
Donepezil, Galantamine, Rivastigmine	6eul, 4ey7	Acetylcholinesterase	Anti-Alzheimer	Nour *et al*. 2024
Benzenepropanoic acid, Cannabichromene, Cannabimoumaronone, Cannabielsion acid	LipOX-2 (PDB ID: 3V99)	Lipoxigenase-2	Anti-inflammatory activity	Metouekel *et al.* (2024)
CBD, Humulene	Alpha-amylase (2QV4)	---	Anti-diabetic Activity	Abchir *et al*. 2023
CBD, Cannabichromene, Cannabidivarin, Cannabipinol, Monopalmitin, Oleonitrile	COX-2 (PDB ID: 6COX)	Prostaglandin synthase-2	Anti-nociceptive activity	Metouekel *et al.* (2024)
Linalool, β-myrcene	TRPV1 receptor	Monoacylglycerol lipase (MAGL)	Nociceptive properties	Alfieri *et al.* (2025)
CBD, CBDA	Nrf2 peptide (PDB ID: 2FLU)	Monoamine-Oxidase-B (MAO-B) Inhibitors	Parkinson's disease	Fantasma *et al.* (2025)
Mesuaferrone B, Piperine, Rivastigmine, Donepezil, THC	7E3H	Acetylcholinesterase (AChE) inhibitors	Neuroprotective activity	Sumontri *et al.* (2025)
CBD	White Spot Syndrome Virus envelop protein (PDB ID: VP28)	---	Antiviral activity	Gunasekaran *et al.* (2025)
Vitexin, Cannflavin, Genistein	1PMN and 1NFI	N-terminal kinase 3 (MAPK10)	Anti-inflammatory activity	Frusciante *et al.* (2025)
Arachidonic acid, Luteolin, Gonodoic acid, Oleic acid	EGFR, SRC, ESR1, HSP90AA1	Phosphoinositide 3-kinase/Protein Kinase B	Anti-diabetic activity	Guzman-Flores *et al.* (2023)

Table 2. Physicochemical properties of bioactive compounds derived from hemp (*Cannabis sativa*).

Compound Name	SMILES	MW	MF	TPSA	logS	logD	LogP	Mp	Bp	pka_acidic	pka_basic
Propanal	CCC=O	58.08	C3H6O	17.07	0.61	0.28	0.18	-77.65	47.81	9.72	4.15
Octane	CCCCCCCC	114.23	C8H18	0	-5.24	3.46	5.05	-87.36	118.68	13.00	6.90
2-methylpropanal	CC(C)C=O	72.11	C4H8O	17.07	0.03	0.77	0.56	-66.85	61.38	9.62	4.58
3-methylbutanal	CC(C)CC=O	86.13	C5H10O	17.07	-0.64	1.22	1.10	-64.42	90.48	8.90	5.30
Ethanol	CCO	46.07	C2H6O	20.23	1.50	-0.58	-0.27	-97.16	87.09	16.10	5.71
Pentanal	CCCCC=O	86.13	C5H10O	17.07	-0.80	1.28	1.32	-78.89	96.63	9.02	5.24
Decane	CCCCCCCCCC	142.28	C10H22	0	-6.22	3.84	5.84	-46.64	169.53	11.53	6.57
(1R)-(+)-α-pinene	CC1=CC[C@@H]2C[C@H]1C2(C)C	136.23	C10H16	0	-4.78	3.67	4.76	-58.80	168.64	11.10	6.96
Trichloromethane	C(Cl)(Cl)Cl	119.37	CHCl3	0	-1.43	1.88	1.90	-60.98	62.14	12.29	5.99
α-thujene	CC1=CCC2(C1C2)C(C)C	136.23	C10H16	0	-3.88	3.13	4.00	-72.83	156.51	10.95	7.21
Hexanal	CCCCCC=O	100.16	C6H12O	17.07	-1.22	1.65	1.68	-63.53	123.64	8.75	5.66
Undecane	CCCCCCCCCCC	156.31	C11H24	0	-6.54	3.91	6.13	-32.44	187.61	11.04	6.55
β-pinene	C1(C2CCC(=C)C1C2)C	136.23	C10H16	0	-3.62	2.94	3.70	-65.87	147.88	10.97	7.45
Sabinene	CC(C)C12CCC(=C)C1C2	136.23	C10H16	0	-3.82	3.01	3.93	-69.63	153.87	10.86	7.38
Ethylbenzene	CCC1=CC=CC=C1	106.16	C8H10	0	-2.73	2.82	3.21	-97.70	137.56	11.76	4.81
1,4-dimethylbenzene	CC1=CC=C(C=C1)C	106.16	C8H10	0	-2.69	3.01	3.08	-40.13	142.13	10.56	6.18
1-undecene	CCCCCCCCCC=C	154.29	C11H22	0	-5.79	3.73	5.63	-61.08	173.16	10.82	6.33
1,3-dimethylbenzene	CC1=CC(=CC=C1)C	106.16	C8H10	0	-2.70	3.09	3.15	-62.35	139.01	10.73	5.68
Myrcene	CC(=CCCC(=C)C=C)C	136.23	C10H16	0	-4.15	3.25	4.37	-88.86	154.17	11.49	6.72
α-terpinene	CC1=CC=C(CC1)C(C)C	136.23	C10H16	0	-3.67	2.99	3.87	-60.32	180.35	10.22	6.28
2-heptanone	CCCCCC(=O)C	114.19	C7H14O	17.07	-1.37	1.83	1.87	-53.64	148.48	9.81	6.16
1-heptanal	CCCCCCC=O	114.19	C7H14O	17.07	-1.71	1.93	2.12	-48.28	150.09	8.51	6.18
Methyl hexanoate	CCCCCC(=O)OC	130.18	C7H14O2	26.3	-1.80	2.14	2.32	-76.19	153.50	9.76	6.46
2-picoline	CC1=CC=CC=N1	93.13	C6H7N	12.89	0.46	0.84	1.11	-37.99	130.48	12.96	5.30
Dodecane	CCCCCCCCCCCC	170.33	C12H26	0	-6.90	4.01	6.49	-22.68	207.72	10.63	6.30
trans-2-hexenal	CCC/C=C/C=O	98.14	C6H10O	17.07	-1.44	1.92	1.91	-66.08	147.97	9.10	6.22
1-ethyl-3-methyl-benzene	CCC1=CC=CC(=C1)C	120.19	C9H12	0	-3.26	3.11	3.74	-88.21	163.29	10.94	5.44
2-pentylfuran	CCCCCC1=CC=CO1	138.21	C9H14O	13.14	-3.81	3.19	4.09	-70.77	177.75	9.96	5.91
Ethyl hexanoate	CCCCCC(=O)OCC	144.21	C8H16O2	26.3	-2.29	2.46	2.79	-76.40	172.71	9.27	6.34
Styrene	C=CC1=CC=CC=C1	104.15	C8H8	0	-2.72	2.76	3.07	-55.75	151.70	10.52	5.75
1-isopropyl-3-methylbenzene	CC1=CC(=CC=C1)C(C)C	134.22	C10H14	0	-3.95	3.32	4.40	-87.24	176.72	11.05	5.68
1,2,4-trimethylbenzene	CC1=CC(=C(C=C1)C)C	120.19	C9H12	0	-3.19	3.21	3.60	-32.37	174.76	10.44	6.10
Terpinolene	CC1=CCC(=C(C)C)CC1	136.23	C10H16	0	-4.26	3.25	4.48	-38.16	185.92	10.14	6.66
Acetoin	C(C(=O)C)O	88.11	C4H8O2	37.3	1.22	-0.52	-0.62	-18.15	150.13	11.67	5.45
Octanal	CCCCCCCC=O	128.21	C8H16O	17.07	-2.32	2.28	2.63	-36.50	168.51	8.34	6.34
Tridecane	CCCCCCCCCCCCC	184.36	C13H28	0	-7.33	4.13	6.93	-13.87	229.33	10.36	6.08
Methylheptenone	CC(=CCCC(=O)C)C	126.2	C8H14O	17.07	-1.72	2.12	2.13	-56.77	165.77	9.60	6.89

Hexan-1-ol	CCCCCCO	102.17	C6H14O	20.23	-1.26	1.82	1.99	-61.24	157.33	10.08	7.12
dimethyl trisulfide	CSSSC	126.3	C2H6S3	0	-1.77	2.20	1.92	-28.89	146.54	8.34	5.57
Nonanal	CCCCCCCCC=O	142.24	C9H18O	17.07	-2.96	2.66	3.18	-25.01	183.53	8.22	6.25
Tetradecane	CCCCCCCCCCCCCC	198.39	C14H30	0	-7.77	4.27	7.39	-5.80	249.62	10.20	5.90
5-ethylcyclopentene-1-carbaldehyde	CCC1CCC=C1C=O	124.18	C8H12O	17.07	-1.81	2.08	2.13	-34.80	160.33	8.45	6.25
1,2,4,5-tetramethylbenzene	CC1=CC(=C(C=C1C)C)C	134.22	C10H14	0	-3.75	3.44	3.87	22.29	195.58	10.47	6.16
ethyl caprylate	CCCCCCCC(=O)OCC	172.26	C10H20O2	26.3	-3.48	3.03	3.80	-54.27	208.87	9.01	6.18
(E,E)-2,4-heptadienal	CC/C=C/C=C/C=O	110.15	C7H10O	17.07	-1.64	1.78	1.83	-5.27	191.85	8.14	4.00
Decanal	CCCCCCCCCC=O	156.26	C10H20O	17.07	-3.44	2.90	3.61	-14.46	196.18	7.91	5.98
Pentadecane	CCCCCCCCCCCCCCC	212.41	C15H32	0	-8.07	4.37	7.72	3.65	268.22	10.15	5.84
Camphor	CC1(C2CCC1(C(=O)C2)C)C	152.23	C10H16O	17.07	-1.73	1.80	1.72	189.75	199.42	8.34	5.33
Benzaldehyde	C1=CC=C(C=C1)C=O	106.12	C7H6O	17.07	-1.22	1.54	1.47	-30.05	179.01	9.65	4.76
Propanoic acid	CCC(=O)O	74.08	C3H6O2	37.3	1.01	0.44	0.44	-8.89	137.87	5.26	6.25
β-caryophyllene	C/C/1=C\CCC(=C)[C@H]2CC([C@@H]2CC1)(C)C	204.35	C15H24	0	-4.29	3.33	4.39	-59.49	169.00	10.96	7.04
Hexadecane	CCCCCCCCCCCCCCCC	226.44	C16H34	0	-8.36	4.46	8.05	9.62	285.06	10.11	5.74
γ-butyrolactone	CC1CC(=O)O1	86.09	C4H6O2	26.3	0.05	0.11	-0.08	-24.42	183.28	7.09	4.49
Phenylacetaldehyde	C1=CC=C(C=C1)CC=O	120.15	C8H8O	17.07	-1.78	1.86	1.70	16.00	197.12	7.14	5.03
4-hexanolide	CCC1CCC(=O)O1	114.14	C6H10O2	26.3	-0.08	0.24	0.29	-39.48	210.12	8.23	4.36
Undecylcyclopentane	CCCCCCCCCCCC1CCCC1	224.42	C16H32	0	-7.89	4.36	7.74	-7.92	278.31	9.30	5.92
β-selinene	CC(=C)[C@@H]1CC[C@]2(C										
CCC(=C)[C@@H]2C1)C	204.35	C15H24	0	-4.04	3.35	4.18	-50.75	176.67	10.24	7.18	
Naphthalene	C1=CC=C2C=CC=CC2=C1	128.169	C10H8	0	-3.47	3.25	3.22	44.60	230.37	9.13	5.21
(-)-γ-cadinene	CC1=C[C@H]2[C@H](CC1)C(=C)										
CC[C@@H]2C(C)C	204.35	C15H24	0	-5.09	4.03	5.39	-106.93	183.92	12.37	5.43	
Hexanoic acid	CCCCCC(=O)O	116.16	C6H12O2	37.3	-1.01	1.68	1.75	-13.75	207.63	4.97	5.34
2,6-di-tert-butyl-4-methylphenol	CC1=CC(=C(C(=C1)C(C)(C)C)O)C(C)(C)C	220.35	C15H24O	20.23	-4.90	3.69	4.93	69.02	251.99	10.38	5.10
2-phenyl-2-butenal	C/C=C(/C=O)\C1=CC=CC=C1	146.19	C10H10O	17.07	-2.26	2.17	2.19	14.52	235.95	8.37	3.98
2-pyrrolidinone	1CC(=O)NC1	85.1	C4H7NO	0	-2.05	2.19	2.32	9.07	158.94	7.18	4.52
Octanoic acid	CCCCCCCC(=O)O	144.21	C8H16O2	37.3	-2.11	2.28	2.80	3.43	238.12	4.86	5.19
Nonanoic acid	CCCCCCCCC(=O)O	158.24	C9H18O2	37.3	-2.69	2.58	3.32	13.54	250.79	4.95	5.00
Methyl palmitate	CCCCCCCCCCCCCCCC(=O)OC	270.5	C17H34O2	26.3	-7.03	4.26	7.29	21.21	301.30	8.13	5.13
4-chlorophenol	C1=CC(=CC=C1O)Cl	128.55	C6H5ClO	20.23	-0.74	2.31	2.58	49.39	215.94	9.34	5.09
trans-methyl linolelaidate	CCCCC/C=C/C/C=C/CCCCCCCC(=O)OC	294.5	C19H34O2	26.3	-6.36	4.01	6.76	-28.58	306.85	7.85	5.30

Ethyl linoleate	CCCCC/C=C\C/C=C\CCCCCCCC(=O)OCC	308.5	C20H36O2	26.3	-6.89	4.39	7.33	-45.03	335.83	9.23	5.30
Methyl linolenate	CC/C=C\C/C=C\C/C=C\CCCCCCCC(=O)OC	292.5	C19H32O2	26.3	-6.05	4.03	6.35	-38.95	322.29	8.38	5.53
(R,R)-2,3-butanediol	C[C@H]([C@@H](C)O)O	90.12	C4H10O2	40.46	1.23	-0.44	-0.51	17.56	180.26	10.49	6.44
4-methyl-2-hexanone	CCC(C)CC(=O)C	114.19	C7H14O	17.07	-1.17	1.66	1.64	-79.13	129.90	10.69	6.19
2-methylbutanoic acid	CCC(C)C(=O)O	102.13	C5H10O2	37.3	-0.20	1.22	1.17	-31.00	178.21	5.10	6.18
methyl (Z)-N-hydroxybenzenecarboximidate	CO/C(=N\O)/C1=CC=CC=C1	151.16	C8H9NO2	41.82	-1.87	2.13	2.15	15.61	212.26	8.86	4.21
1-octen-3-ol	CCCCCC(C=C)O	128.21	C8H16O	20.23	-1.70	2.17	2.40	-54.40	167.80	9.77	6.77
1,3-dichloro-5-methylbenzene	CC1=CC(=CC(=C1)Cl)Cl	161.03	C7H6Cl2	0	-3.70	3.37	4.05	9.68	195.48	8.31	4.77
2,6-dichlorotoluene	CC1=C(C=CC=C1Cl)Cl	161.03	C7H6Cl2	0	-3.57	3.41	3.92	2.28	191.05	8.70	5.09
5-methylundecane	CCCCCCC(C)CCCC	170.33	C12H26	0	-6.16	3.93	5.97	-76.92	183.19	11.32	6.93
butyl benzoate	CCCCOC(=O)C1=CC=CC=C1	178.23	C11H14O2	26.3	-3.49	3.02	3.57	-27.33	250.52	8.84	4.21
(E)-α-bergamotene	CC1=CCC2CC1C2(C)CCC=C(C)C	204.35	C15H24	0	-5.43	3.73	5.32	-52.23	191.80	10.77	7.12
nonylcyclopentane	CCCCCCCCCC1CCCC1	196.37	C14H28	0	-7.13	4.12	6.94	-28.31	249.24	9.56	5.92
CBD (Cannabidiol)	CCCCCC1=CC(=C(C(=C1)O)[C@										
@H]2C=C(CC[C@H]2C(=C)C)C)O	314.5	C21H30O2	40.46	-4.60	4.15	5.54	75.05	333.14	10.01	5.31	
CBG (Cannabigerol)	CCCCCC1=CC(=C(C(=C1)O)C										
/C=C(\C)/CCC=C(C)C)O	316.5	C21H32O2	40.46	-4.56	4.32	6.83	77.52	357.68	9.85	5.32	
THCA (Tetrahydrocannabinolic Acid)	CCCCCC1=CC(=C2C3C=C(C=C										
C3C(OC2(C1)C(=O)O)(C)C)C)O	358.5	C22H30O4	66.76	-3.75	3.07	4.11	148.51	318.29	4.92	3.47	
Linalool	CC(=CCCC(C)(C=C)O)C	154.25	C10H18O	20.23	-1.81	2.34	2.51	-24.00	183.80	9.66	7.29
Humulene	C/C/1=C\CC(/C=C/C/C(=C/CC1)/C)(C)C	204.35	C15H24	0	-5.22	3.66	5.04	5.29	207.36	9.53	6.96
Terpinolene	CC1=CCC(=C(C)C)CC1	136.23	C10H16	0	-4.26	3.25	4.48	-38.16	185.92	10.14	6.66
PEA (Palmitoylethanolamide)	CCCCCCCCCCCCCCCC(=O)NCCO	299.5	C18H37NO2	49.33	-4.49	3.42	4.28	97.91	277.91	7.59	6.81
linolenic acid	CC/C=C\C/C=C\C/C=C\CCCCCCCC(=O)O	278.4	C18H30O2	37.3	-5.13	3.46	6.60	-27.00	355.63	4.89	2.00
Cresol	CC1=CC=CC=C1O	108.14	C7H8O	20.23	-0.75	1.99	1.96	30.63	189.61	10.13	6.25
Octadecatetraenoic acid	CCCCCCCCC/C=C/C=C/C=C/C=C/C(=O)O	276.4	C18H28O2	37.3	-3.73	3.07	4.84	102.00	321.23	4.45	3.32
Hydroxy Octadecatrienoic acid	CC/C=C\C/C=C\C/C=C\CCCCCCC(C(=O)O)O	294.4	C18H30O3	57.53	-3.77	3.41	5.56	-10.89	318.84	4.96	3.15

Palmitoleic acid	CCCCCC/C=C\CCCCCCCC(=O)O	254.41	C16H30O2	37.3	-5.04	3.42	6.23	-0.61	333.48	4.93	3.07
Geranylhydroquinone	CC(=CCC/C(=C/CC1=C(C=CC(=C1)O)O)/C)C	246.34	C16H22O2	40.46	-3.81	3.52	4.79	61.66	311.31	9.43	5.55
Nordihydroguaiaretic acid	CC(CC1=CC(=C(C=C1)O)O)C(C)CC2=CC(=C(C=C2)O)O	302.4	C18H22O4	80.92	-3.68	3.64	3.63	168.46	314.31	8.58	5.48
Nigellic acid	C/C(=C\C(=O)O)/C=C/C1(C(=CC(=O)CC1(C)C)CO)O	280.32	C15H20O5	94.83	-1.99	1.15	0.53	187.00	270.29	3.80	4.39
Geranyl benzoate	CC(=CCC/C(=C/COC(=O)C1=CC=CC=C1)/C)C	258.35	C17H22O2	26.3	-5.48	3.85	5.37	-5.04	306.82	8.65	3.13
Grifolin	CC1=CC(=C(C(=C1)O)C/C=C(\C)/CC/C=C(\C)/CCC=C(C)C)O	328.5	C22H32O2	40.46	-4.68	4.31	6.82	72.08	363.46	9.50	4.83
delta-9-THC	CCCCCC1=CC(=C2[C@@H]3C=C(CC[C@H]3C(OC2=C1)(C)C)C)O	314.5	C21H30O2	29.46	-4.32	4.36	6.15	98.48	346.76	10.12	5.26
dibutyl phthalate	CCCCOC(=O)C1=CC=CC=C1C(=O)OCCC	278.34	C16H22O4	52.6	-4.27	3.62	4.48	-28.28	336.50	8.16	3.89

Table 3. The percentage values along with eigenvalues for all principal component's PCs.

Principal Component	Eigenvalue	Variance Explained (%)	Cumulative Variance (%)
PC1	14.8337	26.716	26.716
PC2	10.2081	18.385	45.101
PC3	6.3844	11.498	56.599
PC4	4.3412	7.818	64.418
PC5	3.9594	7.131	71.549
PC6	3.3044	5.951	77.500
PC7	2.1824	3.930	81.431
PC8	1.9448	3.502	84.934
PC9	1.8463	3.325	88.259
PC10	1.4835	2.671	90.931
PC11	1.1458	2.063	92.995
PC12	0.9593	1.727	94.723
PC13	0.7812	1.406	96.130
PC14	0.6387	1.1503	97.280
PC15	0.3931	0.708	97.988
PC16	0.2828	0.509	98.497
PC17	0.2268	0.4086	98.906
PC18	0.1997	0.3597	99.266
PC19	0.1852	0.3336	99.599
PC20	0.1445	0.2603	99.860
PC21	0.0775	0.1396	100
PC22	8.77E-32	1.58E-31	100

4. Literature Search, Databases and Methodology of Network Pharmacology

Network pharmacology has been a new approach for researching drug mechanisms and creating new drugs due to rapid development of research. TCM network pharmacology studies have been greatly helped in recent years by various related databases and technologies (Zhang *et al*. 2019). In the current literature review, approximately 100 bioactive compounds were obtained from a research paper published by Song *et al*. (2022). According to the procedure described by Ahmad *et al*. (2024), bioactive compounds isolated from medicinal plants were subjected to virtual screening (**Figure 2**) in order to determine important information, such as physicochemical properties, drug-likeness score, bioavailability scores, Blood-Brain Barrier (BBB) permeability, Topological Polar Surface Area (TPSA), and predicted LD_{50}. PubChem, Molsoft, Protox- III database, as well as ADMET screening software, were employed in this analysis. Using the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), The Simplified Molecular Input Line Entry System (SMILES), molecular weight (MW), molecular formula (MF) of the bioactive compounds derived from hemp were obtained. Ye *et al*. (2011) reported that Herbal Ingredient Targets (HIT 2.0) platform was utilized to retrieve medicinal plants directly of utilizing herbal ID to gain potential targets in form of uniport id, protein name, and gene symbol. HIT 2.0 identified 307 potential targets present for *Cannabis sativa*. In addition, these uniport id store information either participates in disease pathways and involved in metabolic processes. For instance, uniport ID (P10635); cytochrome P450 monooxygenase with a role in fatty acids, steroids, and retinoid metabolism. Another protein (Q14330); G-coupled protein receptor (GCPR) with as function in varied physiological processes, especially in immune and nervous systems.

Commonly used database for network pharmacology research include STITCH, String (version 12.0), OMIM database, DisGeNet database, Venny 2.0, TCMD, MINT, Reactome, and Cytoscape reported by (Kunh *et al*. 2014; Szklarczyk *et al*. 2015; Zanzoni *et al*. 2002; D Eustachio 2009; Hamosh *et al*. 2002). Physicochemical properties of bioactive compounds derived from hemp are presented in **Table 2**. Furthermore, copied SMILES or compound name and paste into ProTox 3.0 (https://tox.charite.de/protox3/), an internet web server to find the LD50 value of bioactive molecules, along with data (toxicity model reports) for organ toxicity, toxicity end points, stress response pathways, molecular initiating events, and nuclear receptor signaling pathways. This server displays results as a radar chart and a network chart.

In this literature review, the bioactive compounds derived from hemp were screened for organ toxicity using Protox III. Following the procedure of Mollica *et al*. (2019), 34 out of 100 bioactive compounds were eliminated in initial screening test due to demonstrated neurotoxicity, cardiotoxicity, nephrotoxicity, and respiratory toxicity. Further toxicity endpoint assessment led to the exclusion of 13 additional compounds, indicating potential mutagenicity and carcinogenicity risks.

4.1. ADMET Screening of Hemp Bioactive Compounds

The major goal was to do ADMET analysis and toxicity assessments on the bioactive compounds that we had obtained. Five various pharmacokinetic parameters were computed, and they included Adsorption, Distribution, Metabolism, Excretion, and Toxicity (Alam and Khan 2018). Lipinski's rule is a fundamental requirements of rational drug development. Any drug molecule failing to comply with these rules shows low permeability or poor absorption, according to Dey *et al.* (2023). To address compounds aimed at oral activity, the rule of five (RO5) was formulated. The latter comprises four physicochemical properties: MW < 500 and *LogP* to signify hydrophobicity, H-bond donor < 5, and H-bond acceptor < 10. When these characteristics were considered, 90% of orally active medicines that had proceed to phase II clinical trials showed the presence of these, according to Lipinski (2004). In this literature review, a total of 53 parameters were quantified using ADMET screening (presented in the supplementary file). Drug likeness (DL) $\geq$ 0.18 and oral bioavailability score (OB) $\geq$ 0.30 threshold levels were applied (Daina *et al.* 2017), which were calculated based on data derived from the ADMETlab 3.0 (https://admetlab3.scbdd.com/). Determinants of pharmacokinetics profile include absorption (CaCo-2 permeability, MDCK permeability, PAMPA, pgp inhibitor/substrate, human intestinal absorption (HIA), f20%, f30%, and f50%. For distribution, the parameters which were analyzed including plasma protein binding (PBB), volume distribution (VDss), blood-brain barrier penetration (BBB), fraction unbound (Fu), and inhibitors. Most importantly, the drug with high protein bound (PBB) may have a low therapeutic index. A threshold level of blood-brain barrier score is more than 4, which indicates that a chemical is able to pass a BBB. Similarly, the CACO-2 permeability *LogP* with a value more than -5, defines high permeability of tested chemical, as described by Ahmed et al. (2022). Xenobiotics metabolism entails a diverse array of enzymes families and proteins such as CYP450 enzymes (Mathes *et al*. 2025). Furthermore, in ADMET screening excretion parameters were investigated for CLplamsa and T1/2 for tested drugs. All bioactive compounds were assessed independently for their toxicity, and 22 compounds were found to be exceptionally bioactive and had no harmful effects. Using ADMETlab 3.0 a total of 14 parameters were used to study toxicity profile of bioactive metabolite-derived from hemp. Toxicity profile include hERG blockers, AMES toxicity, rat oral acute toxicity, Skin sensitization, carcinogenicity, eye corrosion, respiratory, human hepatotoxicity, drug-induced nephrotoxicity, ototoxicity, hematotoxicity, genotoxicity, immunitoxicty, and bioconcentration factors (BCF). Principal component analysis (PCA) determines the distribution pattern of variables across coordinates, as illustrated in **Figure 3A**. Principal Component Analysis (PCA) of the ADMET data revealed a cumulative of 100% for the all-Principal components (PCs) with eigenvalues presented in **Table 3**, respectively. Loading score indicated that PC1 were primarily influenced by Plasma Protein Binding (PBB) (0.727) and CYPC19-inh (0.0038), while PC2 were associated with cl-plasma (0.937), fraction unbound (Fu) with loading score (0.091) and PBB (0.075) presented in **Table 4**. PC3 exhibited perecnatge variance of 11.498 and eigenvalue of 6.384, with the most contributing parameters are PBB, Fu and CYP219-inhibitor. The loading scores are recorded 0.653, 0.694, and 0.079, respectively. The ADMET parameters for principal component (PCs) accounted for 7.81% of a variance, with BBB, LogVDss, CYP1A2-inhibitor, and CYP2C19-inhibitor contributing to PC4. This literature review demonstrated that the major contributing PCs retained with a cumulative variance for PCs (PC1 to PC10) > 90%. As shown in **Table 4**, the parameters exhibiting the highest loading scores across PC5 to PC10 are the key contributors to their corresponding principal components. Similarly, the heatmap correlation plot (**Figure 3B**) shows that the parameters labeled in red exhibit a positive correlation with each other, whereas those in blue display a negative correlation.

ADMET analysis are critical for any medicine to be accepted according to Sangkanu *et al*. (2023). Compounds with greater *log-p* make them more lipid permeable and can navigate lipid membranes, enhancing absorption in the body. In **Figure 4A**, chemical compounds are classified into cannabinoids, monoterpenes, sesquiterpenes, aldehydes, alkanes, alkenes, cycloalkenes, alcohols, carboxylic acids, ketones, esters, lactones, hydrocarbons, halogenated-hydrocarbons, phenolic derivatives, and others , which could potentially be implemented later on as potential therapeutic agents against cancer receptor proteins, cardiovascular illness, dementia, respiratory diseases, Covid-19, and gastro-intestinal problems through an in-silico approach. Furthermore, this overview of literature revealed LD_{50} values for the exceptionally all hemp-derived compounds using Protox III (see supplementary file), while the bioactive compounds are presented **Figure 4B.**

Table 4. Loading Score indicating the highest contributing ADMET parameters for PC1 to PC10.

Parameters	PC 1	PC 2	PC 3	PC 4	PC 5	PC 6	PC 7	PC 8	PC 9	PC 10
caco2	-0.003	-0.007	-0.015	-0.007	-0.121	0.133	0.289	-0.186	-0.004	-0.071
MDCK	-0.002	-0.007	-0.011	-0.003	0.000	0.066	0.091	-0.113	-0.002	-0.003
PAMPA	-0.001	-0.064	0.004	-0.251	-0.080	0.048	-0.131	-0.066	0.082	0.120
Pgp inh	0.000	0.012	-0.028	0.100	-0.008	0.081	0.259	0.219	-0.031	-0.400
Pgp sub	0.000	0.003	0.022	0.060	-0.063	0.094	0.017	-0.120	-0.147	0.117
Hia	0.002	-0.005	0.041	0.054	0.131	0.252	0.015	0.124	0.037	-0.142
f20	0.003	0.048	0.061	-0.046	0.202	0.252	0.053	0.224	-0.035	-0.032
f30	0.003	0.047	0.060	0.005	0.278	0.289	0.090	0.250	-0.035	-0.088
f50	-0.002	0.056	0.074	0.002	0.181	0.095	0.087	0.118	0.074	0.210
OATP1B1	-0.001	0.014	0.052	-0.246	0.076	0.155	0.232	0.011	0.093	-0.070
OATP1B3	0.001	0.001	0.034	-0.079	0.181	0.024	0.063	-0.022	0.156	0.020
BCRP	0.002	0.055	0.075	0.012	0.155	0.213	0.087	0.162	-0.032	0.016
BSEP	-0.001	0.020	-0.014	0.146	0.174	0.389	0.178	0.039	-0.178	-0.008
BBB	-0.001	0.005	-0.072	0.274	-0.232	0.013	-0.046	-0.200	-0.175	0.102
MRP1	0.001	-0.003	-0.033	-0.020	-0.104	0.150	-0.179	0.068	0.087	0.009
PPB	0.728	0.076	0.654	0.008	-0.052	0.057	-0.032	-0.072	-0.027	-0.049
LogVDss	0.002	0.020	0.019	0.197	-0.001	0.091	0.005	-0.087	0.316	-0.080
Fu	-0.686	0.091	0.694	0.021	-0.041	0.053	-0.041	-0.080	-0.028	-0.050
CYP1A2-inh	0.003	-0.001	-0.011	0.285	0.273	0.114	0.287	-0.058	-0.309	-0.136
CYP1A2-sub	-0.003	0.003	-0.004	0.037	-0.043	0.034	-0.089	0.104	0.051	-0.241
CYP2C19-inh	0.004	0.025	0.080	0.280	-0.040	0.036	0.422	-0.068	0.305	0.444
CYP2C19-sub	-0.002	0.070	-0.032	0.178	-0.225	0.005	-0.018	0.190	-0.254	0.052
CYP2C9-inh	0.000	0.041	-0.105	0.098	0.233	0.118	0.042	-0.028	0.058	0.235
CYP2C9-sub	0.008	-0.023	-0.047	0.090	0.155	0.150	-0.145	-0.193	-0.409	-0.034
CYP2D6-inh	0.003	0.031	-0.015	-0.013	0.237	0.114	-0.086	-0.116	0.057	0.024
CYP2D6-sub	0.007	0.024	0.093	0.112	0.163	0.212	-0.247	-0.031	-0.106	0.248
CYP3A4-inh	0.004	0.038	0.012	0.085	0.262	0.099	-0.025	-0.038	-0.071	0.247
CYP3A4-sub	-0.001	0.037	0.009	-0.136	0.122	0.323	-0.082	0.243	0.055	-0.126
CYP2B6-inh	0.005	0.025	-0.028	0.074	0.324	0.099	-0.148	-0.247	0.367	-0.192
CYP2B6-sub	0.003	-0.013	-0.016	0.343	0.060	0.002	-0.309	0.034	0.229	-0.204
CYP2C8-inh	0.004	0.031	-0.042	0.187	0.088	0.056	-0.155	-0.137	0.177	-0.001
cl-plasma	0.007	0.974	-0.123	-0.043	-0.091	0.001	-0.020	-0.030	0.000	-0.025
t0.5	-0.006	0.000	-0.036	-0.436	0.051	0.185	0.261	-0.228	0.025	-0.037
hERG	0.001	0.018	-0.004	0.015	0.081	0.017	-0.030	-0.044	-0.081	-0.018
hERG-10um	0.001	0.046	-0.014	0.078	0.095	0.051	0.029	0.037	-0.002	0.039

DILI	-0.002	-0.021	0.010	-0.009	0.006	0.209	-0.078	0.223	-0.040	-0.015
Ames	-0.001	-0.004	0.018	-0.025	0.031	0.004	0.012	0.183	0.038	0.127
ROA	0.000	-0.007	-0.014	0.018	0.020	0.041	0.082	0.109	0.055	0.047
FDAMDD	0.000	0.012	-0.023	-0.037	0.062	0.037	-0.067	0.160	0.020	0.124
SkinSen	0.000	0.024	0.006	0.052	0.010	0.076	0.088	0.032	0.059	0.014
Carcinogenicity	-0.002	-0.011	0.005	0.021	-0.141	0.048	-0.051	0.318	0.117	0.224
EC	0.001	-0.019	-0.019	0.187	-0.168	0.242	0.146	-0.046	0.114	-0.186
EI	0.000	0.000	-0.004	0.013	-0.011	0.024	0.011	-0.014	0.009	-0.018
Respiratory	0.003	-0.016	0.038	0.117	-0.014	0.069	0.117	0.177	0.035	0.007
H-HT	0.000	0.001	0.026	-0.052	-0.024	0.111	-0.083	0.102	0.006	0.050
Neurotoxicity-DI	-0.002	0.000	-0.003	0.067	-0.175	0.034	0.041	0.179	0.131	0.033
Ototoxicity	-0.001	0.012	-0.003	-0.180	0.097	0.069	-0.060	-0.130	-0.062	0.046
Hematotoxicity	-0.001	-0.020	0.012	-0.023	-0.100	0.094	-0.011	0.029	0.044	0.076
Nephrotoxicity-DI	-0.001	-0.024	0.035	0.031	-0.026	0.154	-0.065	0.070	-0.120	0.008
Genotoxicity	-0.001	-0.012	0.049	-0.081	0.051	0.194	-0.037	0.140	-0.066	0.120
RPMI-8226	0.000	-0.001	0.003	0.001	-0.002	0.003	0.000	0.004	0.007	0.000
A549	0.001	0.039	-0.034	-0.074	0.124	0.003	-0.088	0.057	-0.047	0.062
HEK293	0.001	0.023	-0.020	-0.048	0.078	0.012	-0.054	0.057	-0.022	0.054

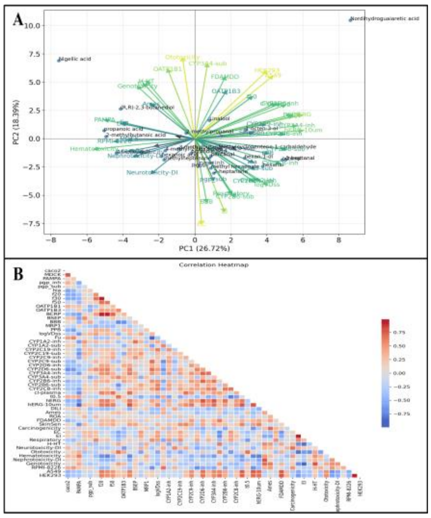


Figure 3. A) Principal Component Analysis (PCA) of ADMET Screening of bioactive compounds derived from hemp, B) Heatmap correction for ADMET parameters.

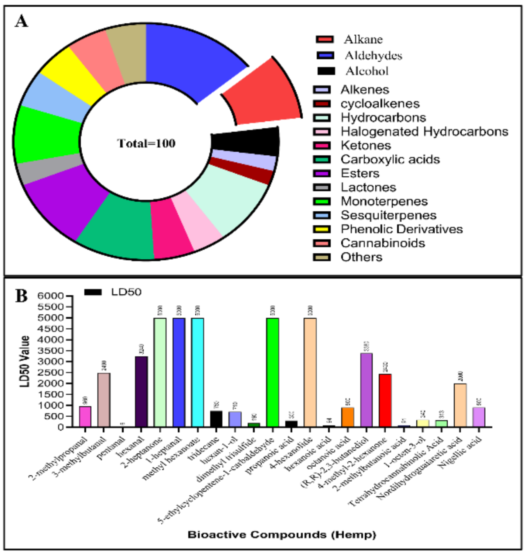


Figure 4. A) Hemp bioactive compound belonging to compound class, B) LD_{50} value of twenty-two bioactive compounds derived from hemp.

4.2. Disease and Metabolites Targets Identification, and Network Construction

In this review, we have focused on disease targets for cancer and diabetes, which were retrieved from databases such as HIT.2, OMIM, GeneCards. Through our literature search, we identified 20,263 disease targets for diabetes and 9710 for cancer, resulting in 7,713 common targets (33.8%). Additionally, metabolite targets were obtained from SwissTargetPrediction software for 22 bioactive compounds retained during the screening process, yielding 1874 targets associated with hemp-derived bioactive compounds in the form of gene symbol or UniProt IDs. Using a Venny 2.0 tool, we construct a Venn diagram to identify common targets between the bioactive compounds (metabolites) and disease targets (cancer and diabetes). **Figure 5A** shared 382 common targets between hemp metabolites and disease.

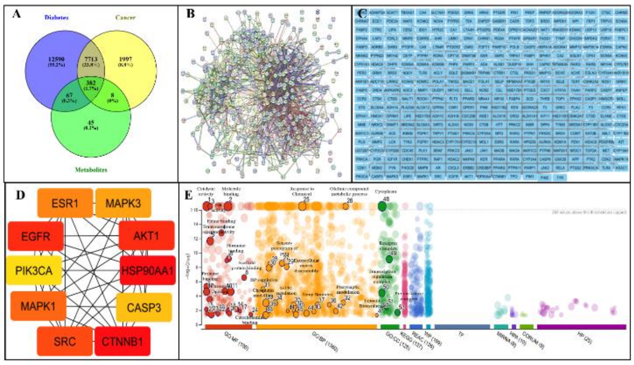


Figure 5. (A) Venn diagram exhibiting common targets for hemp-derived bioactive compounds and diseases, (B) Protein-protein interaction of common targets, (C) list of genes names (common targets), (D) top 10 hubs genes which are associated for both cancer and diabetes, (E) Gene ontology showing the roles of common targets in various metabolic processes.

Table 5. Antimicrobial Potential of *Cannabis sativa* volatile and organic extracts.

Plant Parts Used	Extract Types	Methods Used	Inhibitory Percentage/Zone of Inhibition	Results	References
Leaves	Aqu. Extract	Agar Diffusion Method, Agar Dilution Method	14.55 mm	The results were effective against *Rathyibacter tritici* shows minimal inhibitory concentration of 1%	Kumar *et al.* 2009
Leaves	Ethanolic and Methanolic	Well Diffusion Technique	18 to 20 mm	MIC value of 25mg/mL was reported for E. coli, S. aureus, and Pseudomonas spp.	Essien 2011
Seeds	Essential Oil (EO)	Disk Diffusion Method	16 mm	EO reduce the virulence of *Listeria monocytogenes*	Issepe *et al.* 2019
Hemp hurd Powder	Essential Oil (EO)	Disk Diffusion Method	2mm	No effective results found	Tyagi *et al.*, (2022)
Root powder	Methanolic and n-hexane extracts	CLSI methods	IC50 value of 13.7 µg/mL and 0.8 µg/mL	Ergost-5-en-3-ol and CBD shown a prominent result for antimicrobial potential	Elhendawy *et al.* 2019
Seed oil	Water extract	--	MIC value 3.18 to 6.36 µM	Effectively inhibit the bacterial strains (*E. coli*)	Russo *et al.* 2021
Inflorescence	Aqueous extracts	Broth dilution method	MIC values of 3.57 and 7.14	Plant extract shown promising antimicrobial properties against *S. aureus* and *E. coli*	Ferrante *et al.* 2019
Inflorescence	Aqueous and methanolic extracts	Agar well diffusion method	MIC values ranges from 0 to 7 mm for aqueous and 0-19 mm for methanolic extracts	*B. cereus* showed highest zone of inhibition 19.5 mm at 70% MeOH	Motiejauskaite *et al.* (2023)
Leaves	Ethanolic extract	Disk diffusion method	MIC values ranges from 7 mm to 18.7 mm	Crude leaves extracts are effective against *S. aureus*	Roshan *et al.* (2024)
Seed oil	Ethanolic	Disk diffusion method	Lowest MIC value of 9 mm	*K. pneumonia* was found least sensitive to CSEO	El-Mernissi *et al.* (2024)
Root	Ethanolic extract	Microbroth dilution method	MIC values for *S. aureus, E.coli* & *P. aeruginosa* are 39 mm, 38 mm and 36 mm, respectively	AgNPs synthesized from hemp root effected gram-positive bacteria more than gram-negative	Suman *et al.* (2022); Yologlu *et al.* (2025)
Seed	Ethanolic and n-Hexane extracts	Microdilution method	MIC value of 23 mm and 7 mm	Ethanolic seed extracts are effective against Penicillium sp.	Haddou *et al.* (2023)

We then used STRING software to generate protein-protein interaction (PPI) plot for these common targets (**Figure 5B**). Further interpretation of PPI network was performed using Cytoscape (3.10.3), revealing 382 nodes (each representing a target) and 1725 edges as shown in **Figure 5C**. The network density was calculated to be 0.028, with a clustering coefficient of 0.408. Using the degree method, we identified top 10 hub genes/proteins associated with both cancer and diabetes: CTNNB1, EGFR, AKT1, SRC, MAPK1, ESR1, MAPK3, CASP3, HSP90AA1, and PIK3CA (**Figure 5D**). Furthermore, gene ontology analysis of common targets revealed their role in various metabolic process across molecular function (MF), biological process (BP), and cellular component (CC) as illustrated in **Figure 5E**.

4.3. Antimicrobial Potential of Hemp (Cannabis sativa L.)

Hemp seed oil gaining popularity in medicine and research considering to its antibacterial activity against a variety of bacteria and fungus caused disorders (Ostapczuk *et al*. 2021). Natural resources like plants are precious, offering phyto-active/bioactive compounds, lignocellulosic biomass, and a wider variety of fiber types. An important goal in hemp fiber quality improvement is a genetic engineering application widely used for improving trait quality and lignocellulosic biomass (Andre *et al*. 2016). Prior findings revealed that hemp bast fiber has a greater antimicrobial potential and is frequently used for antibacterial finishing agents by Khan *et al*. (2015). In major hemp ingredients, bast fiber is abundant in terpenes and sterol derivatives associated with β-sitosterol and β-amyrin (Gutierrez and Rio 2005). According to Khan *et al*. (2015) demonstrated that hurd fibers contain more lignin than bast fibers, which are effective against *Escherichia coli*. Another research study of Issepe *et al*. (2019) described that hemp is source of essential oil and examined for antimicrobial potential. According to Farha *et al*. (2020) observed that cannabinoids at 2 µg/mL effectively suppress *S. aureus* biofilm development, with cannabigerol (CBG) at 4 µg/mL scattering established biofilms and eradicating per-sister colonies. A total seventeen different (EOs) from hemp were tested for antimicrobial activity, among them a highest (MIC) of 16 mm and 32 mm noticed for *Listeria monocytogenes*. In literature, previous studies had published shown an interesting outcome for antimicrobial efficiency using hemp plant parts such as (leaves, inflorescence, seeds, oil, and EOs) in various extract (aqueous, ethanol, methanol, acetone, n-hexane, petroleum ether, and acetone). A Mathur *et al*. (2013) had noticed that hemp shows a promising result of antimicrobial efficacy for *P. aeruginosa* and *P. aureus*, inactive against *E. coli* and *C. albicans*. The public's growing awareness of antibiotic overuse and the controversies regarding developed antibiotics/drugs brought back interest in naturally antibacterial plants (Khan *et al*. 2014). Hong *et al*. 2022 described the findings of collaborators, (2019), who estimated that bacterial antibiotic resistance caused 4.95 million deaths in 2019. Meanwhile, Antibiotic resistance is an issue to human health, however herbal remedies containing biologically active substances and antibacterial capabilities may provide assistance. Hemp products strengthen the immune system and can be consumed as nutritional supplements (Ahmed *et al*. 2008). Interestingly, Dynamic maceration (DM) is a relatively frequent method for extracting antibacterial activities from hemp plant parts. Plant can be soaked in a solvent and agitated to extract biologically active compounds. These active chemicals in plants are profoundly related to the solvent utilized for extraction and their antibacterial abilities (Fathordoobady *et al*. 2019). **Table 5** shows that various extracts made from plant parts using specific procedures produce exceptional outcomes for antimicrobial properties.

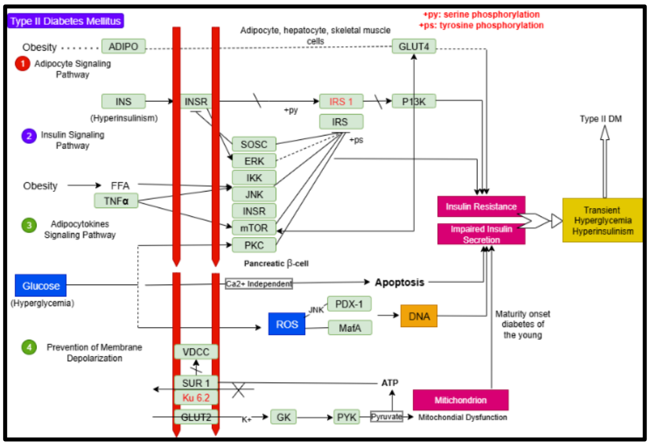


Figure 6. Schematic representation of the adipocyte signaling pathway, insulin signaling pathway, and adipocytokine signaling pathway. This mechanism presents the activation of PKC, further binding of insulin-to-insulin receptor substrate (IRS) resulting in phosphorylation of serine and tyrosine. This raises the quantity of phosphatidylinositol-3,4,5-trisphosphate, which attracts Akt to the plasma membrane alongside phosphatidylinositol-dependent kinase 1 (PDK1). In this cascade, PDK1 phosphorylates Akt at Thr308 and mTORC2 at Ser473. The active CB1R activates extracellular regulated kinase (ERK) and p38 mitogen-activated protein kinase (MAPK), which then suppresses IRS1 phosphorylation at Ser 307. Activated CB1R is also thought to limit the activation of mTORC2, blocking Ser473 phosphorylation of Akt.

4.4. Antidiabetic Activity

Diabetes mellitus (DM) is a long-term metabolic illness characterized by persistently elevated blood glucose levels and abnormal lipid, carbohydrate and protein metabolism (Gowd *et al*. 2018). It is considered to be a widely prevalent medical conditions in around the world. In accordance with Haddou *et al*. (2023), the worldwide prevalence of diabetics will probably exceed 552 million by 2030. Hyperglycemia is a hallmark of type 2 diabetes which is caused by insulin resistance and pancreatic b-cell dysfunction. In adipocyte signaling pathway revealed that insulin resistance is primarily caused by excess fat around the belly (visceral fat). This implies that cell of body fails to respond to insulin efficiently, and the pancreas is unable to secrete sufficient insulin to counteract it (Campbell and Newgard 2021). Silva *et al*. (2017) reported that people with obesity may experience the release of free fatty acids

(FFAs) from adipocytes and pro-inflammatory molecules (adipokines). Adipokines like TNF-α have an important role in triggering insulin resistance. These molecules can disrupt insulin signaling pathways in a number of tissues such as muscles, liver, and fat cells. In insulin resistance, the usual signaling cascade initiated by insulin binding to its receptor (INSR) is compromised (Kojta *et al*. 2020). This can entail abnormalities in the phosphorylation of insulin receptor substrate (IRS) proteins, which are transmitting the insulin signals within the cells (Ibrahim 2010). According to Itani *et al*. (2002) demonstrated that the phosphorylation of IRS directly activates phosphoinositide 3-kinasse (PI3K) mandatory for normal insulin function. There are several aspects of visceral adipose tissue (VAT) that differentiate it from subcutaneous adipose tissue (SAT), including its morphology and function. Different tissues can cause dysfunction in lipid and glucose metabolism. Kojta *et al*. (2020) revealed the impaired mitochondrial function, resulting in ectopic fat storage and elevated triglycerides in the liver and muscles, can account for obesity-related insulin resistance present in **Figure 6**.

People with Type 2 diabetes must use hypoglycemic medications or insulin ingestion to regulate consistent blood sugar levels (Harrower 1994). In diabetics, lower production of the incretin hormone GLP-1 is regulated by the uptake of antihyperglycemic medication dipeptidyl peptidase-IV (DPPIV) antagonistic peptides. Drugs prescribed for managing diabetes, including vildagliptin, sitagliptin, and linagliptin, may have significant side effects (Thongtok *et al*. 2024; Bounaas *et al*. 2024). DM increases the risk being diagnosed with some cancer’s types particularly breast cancer (Damsud *et al*. 2024). Earlier research by Wolf *et al*. (2005) found that up to 10 to 20% of individuals diagnosed with breast cancer were also experiencing diabetes. In addition, it may result in several other serious complications such as eye damage, renal failure, fool ulcer, and cardiovascular diseases (CVDs) in accordance to Rakha *et al*., (2024). This has spurred a renewed belief in herbal remedies as a way to mitigate the negative repercussions (Campbell *et al*. 1996; Haddou *et al*. 2023). The computational approach is target-based drug discovery approach widely employed since it provides correct results while also saving time and money. Several experiments have been conducted to produce novel diabetic medications by targeting phytochemicals against specific receptor proteins such as GLP-1, SGLT2, AR, PPAR-c, GPR40, and DPP4 are being clinically tested (Chauhan *et al*. 2023). DPPIV inhibitory proteins synthesized from diverse plants (jack bean and macadamia) are more practicable and less costly than those produced from animal sources (Sharma *et al*. 2020). Hemp is an important source of protein, ranging from 20-25% depending on climatic circumstances. Edestin (a globular protein) is prominent seed proteins, subsequent to albumin and vicilin (Sun *et al*. 2021; Capcanari *et al*. 2024). Thongtok *et al*. (2024) stated that hemp possessed effective hypoglycemic peptides from seeds hydrolysate, although they were discovered to impede α-glucosidase instead of DPPIV. Among the most common a-glucosidase inhibitors are acarbose, miglitol, and voglibose reported by Joshi *et al*., (2015). Suttithumsatid *et al*. (2022) have noticed that CBD in hemp typically carrying multiple activities including modulating glucose homeostasis, facilitating insulin secretion, lowering AGE levels, and inhibiting α-glucosidase activity. Another study by Alam *et al*. (2022) indicated that polyphenol chemicals (cannabisins and cannaflavins) in hemp have antioxidant characteristics and may help to control blood sugar levels and improve insulin sensitivity, making it a potential alternative for diabetes management. Beta-caryophyllene was demonstrated to significantly lower glucose levels in rabbits by Naz *et al*. (2023) and to offer promise in preventing hyperglycemia-induced dyslipidemic complications. Furthermore, a dosage concentration of 1.2 mL/kg exhibited a maximum decrease of 243.4 mg/100 mL. The mechanistic representation of antidiabetic activity is given in **Figure 6**.

4.5. Anticancer Activity

Hemp's phytoactive compounds hold a captivating anticancer efficacy. Hemp and marijuana include stilbenoids of ten types, which are phenolic compounds with antioxidant properties and can inhibit cancer cell proliferation (Kundan *et al*. 2022). Previous research indicates that whole hemp plant extracts are more powerful fighting to cancer cells than individual cannabinoids. Bram *et al*. (2019) validated this finding, noting that plant extract promotes cancer cells slaying at higher rates than pure THC. Moreover, when equal concentrations of THC and numerous plant extracts were used, the survival of different cancer cell lines varied. Cannabinoids (CBD) is the second-most prominent cannabinoid in hemp, does not have the negative consequences associated with Δ9-THC, such as drug reliance, tolerance, and misconduct. CBD engage pro-apoptotic pathways, allowing them to cause apoptosis (programmed cell death) avoiding damaging healthy cells by selectively targeting the endocannabinoid system (Lile *et al*. 2013). It functions as a transmission networks, which is critical for sustaining homeostatic equilibrium. It controls multiple physiological processes such as immunomodulation and synaptic transmission. The endocannabinoid system is partially activated by the attachment of endo-, phyto-, or synthetic cannabinoids to cannabinoid receptors (CB), which are representatives of the seven-transmembrane G-protein coupled receptor (GPCR) family. The CB1 receptor is prominently expressed within the brain, including the hippocampus, basal ganglia nuclei, cortex, and cerebellum. CB2 receptors can be expressed in both cell types (macrophages and leukocytes) and organ types, such as the lungs and testes reported by McAllister *et al*. (2021). THC may bind to CB1 and CB2 receptors, which govern different physiological activities such as drowsiness, hypothermia, pain relaxation, locomotor activity reduction, and hunger augmentation (Duggan 2021). Furthermore, the CBD binds to CB1 as a blocking agent and may inhibit THC activity. The detailed mechanism of anti-cancer activities was presented in **Figure 7**. Cannabinoids such as THC, CBD, and CBG engage with these receptors to activate a variety of intracellular signaling cascades that influence cell fate choices. THC and CBD may activate CB1 and CB2 receptors, which can modulate numerous signaling pathways (**Figure 7**). The activation of the ERK1/2 pathway leads to the overexpression of cyclin-dependent kinase inhibitors p21 and p27, which causes cell cycle arrest by inhibiting the phosphorylation of the retinoblastoma protein (pRb). This procedure halts the cell cycle. Additionally, stimulation of the PI3K/AKT pathway influences cell proliferation and autophagy via mTORC1. Prolonged activation of the PI3K/AKT pathway may cause endoplasmic reticulum (ER) stress and the activation of cellular stress indicators such as ATF4, TRIB3, and CHOP, which can result in apoptosis. CBG interacts with the TRPV1, TRPV2, and TRPM8 receptors, causing the release of reactive oxygen species (ROS). The buildup of ROS activates proapoptotic proteins, inducing programmed cell death.

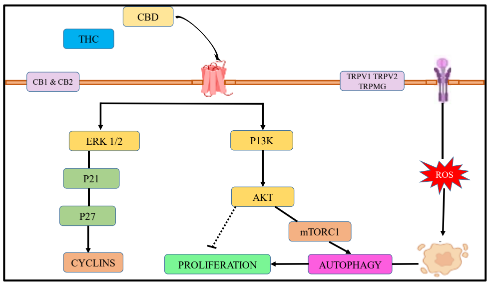


Figure 7. Molecular pathways mediated by cannabinoid receptors in cancer cells. This figure depicts the molecular pathways mediated by cannabinoid receptors CB1 and CB2, as well as TRPV1, TRPV2, and TRPM8 in cancer cells.

This counter action is speculated to mitigate the negative side effects of THC counselling, such as intoxication, rapid heart rate, stress, and drowsiness. Afrin *et al*. (2020) found that CBD is not harmful to patients, even at large dosages, unlike Δ9-THC, which has a recommended daily intake of just 15 to 90 mg in adult patients. A daily adjustment is necessary in order to ensure that the side effects of each patient are treated appropriately. CBD reduces cell proliferation, promotes apoptosis, and decreases proliferation of cells, metastasis, and angiogenesis in numerous cancer types, both in vitro and in vivo according to McAllister *et al*., (2021). On other hand, the main concern with chemotherapeutic medicines is that they frequently have significant adverse reactions, targeting both normal, healthy cells and malignant cells. This problem might be solved by using natural chemicals or mixes that have extremely few and moderate side effects whilst both demonstrating anticancer capabilities and/or mitigating chemotherapy fallout (Petrovici *et al*. 2021).

5. Legalization and Restrictions on use of *Cannabis* sativa

The use of hemp (*Cannabis sativa*) for research and medicinal reasons is permitted inside the border of nations that have ratified international drug control agreements (de Souza *et al*. 2022). The most significant of the stringent laws needed to accomplish, this is the establishment of several federal agencies charged with monitoring the unlawful trade of medicinal hemp and reporting to the International Narcotics Control Board (INCB) documented by Aquilar *et al*. (2018). Furthermore, national hemp institutions are given exclusive authority to maintain inventory of collected plant material and manage it for marketing (Health Products Regulatory Authority 2017). Further, cannabis-derived drugs must be prescribed and delivered under doctor supervision, contingent on assurance of its safety, potency and efficacy (European Monitoring Centre for Drugs and Drug Additions 2018). One of the primarily strategies implemented by nearly all countries for lowering cannabis use is legal banning. Legal bans appeared to have substantially lowered cannabis use in several countries, (Kathmandu for instance, was considered a 'hippie hub' attracting tourists without legal constrains, which had in turn bolstered hashish and tourism). Some countries, like Spain have more lenient rules than others such as Malaysia. The Spanish penal code (section 368), distinguished between medications that do significant harm to a person's health and those that do not (Arana 2019).

The US government revoked a 26-state ban on the utilization of cannabis drugs and products for leisure and medicinal purposes. The major concerns of these opinions are the future legalization and decriminalization of cannabis, together with health advantages of smoke cannabis, are being advertised in ways that bypass the FDA routine testing and regulatory protocols, otherwise mandated for all drugs sold for human consumption in US (Svrakic *et al*. 2012). This knowledge is key to legalization of cannabis such that nothing the government does increases the cost of cannabis as much as prohibition, having a negative impact on the business (Caulkins and Reuter 1998). As a result, state after state experienced financial crisis after the prohibition of cannabis was repealed. Wholesale prices within four years fell down by 70% in Colorado, for instance, the price drops in Washington and Oregon have been more pronounced (Humphreys 2017). Shover and Humphreys, (2019) reported that legal charges are slowly decreasing by about 1%, and one day they will be low as a penny per joint, matching the price of beer nuts, which are free at restaurants and bars.

In the US and European countries, the legal age for purchasing alcohol and cannabis is 21. Many jurisdictions also set possession limit of 28.5 grams of cannabis for adults (Quinn 2015). According to recent enacted law, Smart *et al*. (2017) reported that product made from cannabis are subjected to taxes in almost all US states, with rates ranging significantly. Current body of literature suggested that Uruguay became the first country to legalized the consumption of cannabis derived products recreationally in 2013. Adults were permitted to consumes the cannabis in three ways, 1) they cultivate cannabis at domestic level; 2) if they are an authorized member of licensed club; 3) if they are registered user to pharmacies approved by regulatory authorities (Hall and Lynskey 2020). **Table 6** presented current status on legalization and decriminalization on usage of cannabis across different countries.

Table 6. Legalization and Prohibition on use of cannabis countries-wise status.

Country	Legalization	Decriminalization	Domestic Production	Recreational Purposes	Medicinal Applications	References
Thailand	Yes	Act (108/57) from NCPO in 2014, to decriminalize all drug use	Allow	THC legalized for recreational purposes	Drug act passed in 2019 for cannabis for medicinal purposes with prescription.	Kalayasiri and Boonthae, (2023)
Thailand	Yes	Revised act in 2022	Allow	THC addition in food and drinks	In June 2022, TMWPH act passed, restricted younger than 20 years and pregnant women to use drugs	Kalayasiri and Boonthae, (2023)
Pakistan	No	No	Restricted	Use as sedative and narcotic effect	To treat anodyne, tonic and wound healing	Saqib *et al*. (2025)
Nepal	No	No	Restricted	Use as sedative	Ethnoveterinary remedy	Bonini *et al*. (2018)
Netherlands	Yes	Yes	Allow	Supply in coffee shops	To treat numerous diseases	Raufer, (2024)
Morocco	Yes	UNODC reported this country is leading producer in 2020	Allow	Use for leisure	Experimental trails against numerous diseases	Dalli *et al*. (2023)
Algeria	No	Illegal	Prohibited	Recreational purposes	Majority consumes as a psychoactive substance	Junior *et al*. (2023)
Angola	Illegal	Illegal	Prohibited	Use of cannabis is Punishable by law	Does not recognized any industry	Kitchen *et al*. (2022)
Burkina Faso	Illegal	Illegal	Prohibited	Current status (unclear)	Current status (unclear)	Junior *et al*. (2023)
US	Legal in many states	Partial prohibition	Restricted in federal areas	Use cannabis for recreational purposes	Extensively use for medicinal and research purposes	Shi *et al*. (2015)
Croatia	Illegal	Prohibited	Punishable offense	High restriction of use of cannabis	Use for medicinal purposes	Room, (2010)
India	Partial	Partial prohibition	Parvati valley generated over 2000 hectares of cannabis (NCB report 2013)	Cannabis by-products are ganja, charas, and bhang	Uses for medicinal, and religiously nationwide	Chouvy, (2019)
Thailand	Yes	Yes	Licensed from authorities, domestic production allowed in 2020	Use for pleasure	To treat epilepsy, Parkinson disease, cancer and demyelinating	Ransing *et al*. (2022)
Iran	Illegal	Prohibited	Punishable offense	Stickley prohibited on use and trafficking	Use of Dronabinol capsules and 'Sativex' for some research projects	Boujraf, (2020)
Germany	No	No	No	Prohibited the purchase of recreational cannabis	Use for production of medicinal cannabis products	Ransing *et al*. (2022)
South Africa	To be ratified by parliament	No	Restricted the domestic production	Use as sedative	Permitted for research only	Riley *et al*. (2020)

6. Clinical Applications of Cannabis-Derived Drugs

Historically, hemp (*Cannabis sativa*) has been consumed for millennia because of its considerable medicinal potential, whether it is consumed as extracts or as a combination with several cannabis metabolites (Schultes and Hofmanns 1992; WHO 2018). WHO reported that, the administration of CBD is effective to treat epilepsy proven through clinical trials.

1. In humans and animal trials, cannabidiol (CBD) has been shown to be effective in preventing and lessening seizures, particularly those induced by Dravet syndrome, a severe juvenile epilepsy with high fatality. The US Food and Drug Administration (FDA) officially approved 'Epidiolex', a drug derived from CBD as an effective and safe treatment for seizures (FDA 2020).
2. Food and Drug Administration (FDA) has also approved synthetic-THC drug 'Cesamet, Syndros, and Marinol' to treats AIDS-related anorexia, chemotherapy-induced cancer, and vomiting (Simiyu et al. 2022).
3. United Kingdom's National Institute for Health and Care Excellence (NICE) has released a recommendation for the utilization of CBD and THC-containing drugs in treating of numerous aliments such as chronic nausea, and treatment-resistant epilepsy (Lennox-Gastaut syndrome and Dravet syndrome (UNICE 2019).
4. Therapeutic Goods Administration (TGA) approval is required in Australia, to define a dose limit to individual patients or groups of patients who suffered with same condition. Sativex and Epidiolex are approved medicines utilized to treat several disorders including sclerosis, nausea, cancer, anxiety and epilepsy. The doctor can in any event prescribe a pathology other than those for what it is indicated (Baratta et al. 2022).

In this literature review, we concluded the clinical studies outcomes across different nations varies in terms of dose administration path, medicine, number of volunteers, disease condition, and study type reported by Baratta *et al*. (2022). According to the past literature, the research by Baratta *et al*. (2022) showed that cannabis-based medicines (CBD, THC, Sativex, and Bedrocan) were subjected to commonly used conditions for research such as epilepsy, nausea, severe behavior disorders, chronic pain, pharmacokinetics, fibromyalgia, psychosis, drug-resistant epilepsy, drug addiction, and peripheral neuropathy. In this review we summarized the results of 18 trials with an affirmative clinical outcome for all, i.e., UK (5), Australia (4), US (4), Israel (4), and Switzerland (1). Sample size considerably ranges from 8 to 128 enrolled subjects in these trials. In most studies, 12 administered CBD with a standardized dose, whereas 6 examined herbal derivatives of cannabis and authorized medicines. These trials implemented methods of administrations of products to be administered orally, inhaled and injected. In general, CBD proved to be effective in treatment of various diseases, while investigation with herbal cannabis preparations is concerned mainly with the issues of pain, vomiting, brain activity and cannabis dependence. Most commonly, THC and CBD were administered in different ratios, whereas in few cases THC content herbal cannabis preparation was applied (Almog *et al*. 2020; Efron *et al*. 2020; Freeman *et al*. 2020; Xu *et al*. 2020).

7. Adverse Drug Reaction (ADRs)

In 1960, THC was reported for the first time in *Cannabis sativa*, and were thought to a greater medicinal value which was actually not. Consumption of the drug later led to psychomotor impairment, which could cause low self-control and lead to serious health effects. There is significant evidence that cannabis use during pregnancy can cause fetal harm, particularly in weight growth, and may elevate the risk of certain cancers later in life (WHO 2023). Several potential harmful effects of CBD use on the male reproductive system have been linked to long-term use, including testicular atrophy, liver damage, and interactions with certain drugs. It has been observed by Koller *et al*., (2015) that normal individual lymphoblasts, CBD show carcinogenic characteristics and can cause damage to DNA at doses ranging from 25 to 50 µM. However, the illness burden associated with pleasure-seeking consumption of hemp is substantially lower than that of other frequently smoked legal and illegal drugs (Imtiaz *et al*. 2012). The effects of cannabis on memory, brain structure and cognitive function are thoroughly reviewed by Burggen *et al*., (2019). Based on the previous literature, the usage of cannabis for pleasure has long-lasting consequences on brain morphology and thinking abilities, with the effects probably being more noticeable in teenagers. The study of Ginsburg, (2019) revealed that it is hard to claimed that cannabis use has in adverse impact on driving in either way. Cannabis clearly elevates driving impairment, but it is unclear if this condition is severely enough to raise the risks of car accidents. The finding of Ewing *et al*. (2019) performed in-vivo activity on mice model, in which they provide evidence for hepatotoxicity of CBD. Oral CBD delivery at 2460 mg/kg per day or 615 mg/kg (10 days) exhibited a detrimental effect on liver tissue and enzymes such as plasma alanine aminotransferase and aspartate aminotransferase. Surprisingly, the information acquired thus far is unclear; yet, it is predicted that prenatal exposure to hemp could lead to neurocognitive consequences, namely causing mental diseases (anxiety and depression) and attention deficit hyperactivity problems (Roncero *et al*. 2020). For CBD products to be used correctly and safely, precise regulations must be enacted and enforced (FDA 2023). Wishart *et al*. (2006) reported Drug bank (http://go.drugbank.com) is an online platform to verify the status of drug, indicating whether it is in the investigational stage or approved by FDA or other regulatory authorities. This tool is valuable because it provides comprehensive information on each drug, including its release date, marketing status by country, recommended dosages, administration routes, metabolism, half-life, and mechanism of action.

8. Concluding Remarks, limitations and Future Prospects

Hemp (*Cannabis sativa* L.) is becoming multipurpose crops with great industrial, medicinal and food value. To systematically explain the mechanism of action of metabolites-derived from *Cannabis sativa* L. in the treatment of cancer and diabetes, network pharmacology and *in-silico* approaches were employed to explore active compounds, targets of Cannabis against diabetes and cancer and the related signaling pathways. A total of 100 metabolites-derived from Cannabis and 8095 of their targets were predicted by multiple databases. Meanwhile, 9710 cancer-related and 20,263 diabetes-related targets were screened by multiple databases. By statistical interaction, a total of 382 common targets were obtained. Gene ontology (GO) analysis indicates that these potential targets are participated in multiple molecular pathways such as hormone binding, catalytic activity, molecule binding and protein binding. The metabolites interact with targets (EGFR, AKT1, SRC, MAPK1, ESR1, MAPK3, and CASP3) to inhibit the progression of diabetes and cancer in signaling pathways. This study provides a practicable strategy for the development of new Cannabis drugs for cancer and diabetes. Further, this work systematically deciphered the possible mechanisms of Cannabis in cancer and diabetes management through network pharmacology approach for the first time and thus provide a valuable insight into future experimental and clinical research. Future research should focus on exploring the ‘‘entourage effect’’ where terpenes and cannabinoids acts synergistically to enhance therapeutic efficacy rather than isolating individual compounds. Advancing the concept through crop-bioengineering, nanotechnology-based delivery system and pharmacological synergy represent a promising future direction to fully optimize the therapeutic potential of hemp.

Authors Contribution

All the authors contributed equally in this final draft of manuscript. This draft was validated, finalized by all the authors for submission.

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Conflict of Interest

All the authors declare no competing interest.

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