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Review

Volatile Organic Compound–Drug Receptor Interactions: A Potential Tool for Drug Design in the Search for Remedies for Increasing Toxic Occupational Exposure

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Abstract: Volatile organic compounds (VOCs) can impact the actions of drugs due to their effects on drug receptors and the activities of enzymes involved in various metabolic processes, especially those relating to gene regulation. They can disrupt cellular functions and potentially affect human drug metabolism and utilization receptors. They mimic or inhibit the actions of endogenous ligands, leading to carcinogenesis, neurotoxicity, endocrine disruption, and respiratory disorders. Chronic exposure to VOCs due to human occupation can lead to an increased generation of reactive oxygen species (ROS), which could lead to oxidative stress and damage to lipids, affecting the formation and proper functioning of gene regulation, enzyme activity, and cell membranes. The presence of oxidative stress could interfere with drug activity and potentially impact the body's ability to process and utilize drugs effectively. This is because drugs such as antioxidant drugs play an essential role in cell protection against oxidative damage. Therefore, disruptions in their metabolism could distort the overall health condition through the breakdown of antioxidant defense mechanisms. In this study, the aim is to assess the effect of VOC exposure on drug receptors and the way forward in designing and maintaining optimal drug activity for workers' overall well-being.

Keywords: drug receptor; drug design; enzyme; VOCs and ROS

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1. Introduction

Humans spend half of their life span in the occupational setting, making them endangered due to the effects of various occupational hazards in the form of volatile organic compounds (VOCs). The results are due to the cumulative effects associated with long-term exposure. These workers face VOC fumes from different chemicals as they carry out

their day-to-day primary assignments [1]. Different profiles of VOCs are emitted in the workplace, depending on the nature (concentration), method of application, and the type of chemicals used. Indoor workers, such as workers in paint production industries, spraying workshops, cement factories, quarry centers, and those exposed to petrochemical fumes, are suspected to be highly affected by certain kinds of VOCs [2]. Work plays a central role in people's lives socially, economically, and health-wise. It shapes workers' lives as they spend at least eight hours or more in their workplace [3].

Occupational exposure to VOCs involves the conscious or unconscious subjection of workers to potentially hazardous or harmful chemical fumes that are naturally or anthropogenically generated as a result of their work. Occupational exposure encompasses the risks, harm, and danger that workers face in their workplace [3], and is a form of occupational pollution. Low levels of education among workers, poor knowledge of health hazard precautions, the unavailability of preventative measures, globalization, and rapid industrial growth in the past decades have added more complex issues relating to occupational health challenges [4]. About 2.9 billion workers are exposed to various types of hazards. Daily, workers are faced with various hazards depending on their work, ranging from biological and chemical to mechanical hazards [5].

VOCs can alter pharmacodynamics by interfering with drug and receptor interactions, thereby impacting the outcome and safety of drugs. Knowledge concerning VOCs and how they change these interactions can pave the way for the production of new medications that can neutralize the toxic impacts of VOCs [6]. Such an approach may improve the diagnosis and control of ailments related to work exposure to poisonous substances, which can be monitored with biomarkers. Biomarkers are essentially biological compounds or molecules, such as enzymes, hormones, or reaction by-products found in the body's cells, tissues, or organs, whose presence and/or concentration indicate the body's well-being or otherwise. They can be used to analyze the progression, diagnosis, and assessment of the health of workers exposed to VOCs. Through VOC–receptor interaction, it is possible to come up with non-invasive diagnostic procedures such as lung breath analysis to check for the first hints of toxic substances, thereby enhancing the regular monitoring of workers' health to prevent more severe health issues in the future [6].

2. Volatile Organic Compounds (VOCs)

Volatile organic compounds (VOCs) are a group of chemicals emitted from thousands of commonly used products in the workplace. They are characterized by high volatility and mobility—properties that allow them to easily vaporize when exposed [2]. They are released from a wide array of products such as paint, wax, varnish, agricultural products (pesticides, herbicides, and insecticides), different laboratory solvents, wood preservatives used in furniture making, and office equipment such as copiers and printers [7]. VOCs are chemically composed of carbon, with one or more functional groups such as oxygen, phosphorus, nitrogen, silicon, halogen, and sulfur [8]. They are also a product of natural discharge during volcanic eruptions [9]. They are grouped into aromatic hydrocarbons (benzene, xylene, toluene, formaldehyde, and ethyl benzene) and halogenated hydrocarbons (chloroethylene, trichloroethylene, and vinyl chloride), the latter group being more toxic compared to the aromatic group [10]. Volatile organic compounds are a class of organic chemicals generally classified into VVOCs, VOCs, and SVOCs due to their high volatility when exposed.

VVOCs represent the most dangerous class of volatile organic compounds encountered in occupational settings (Table 1). They are very toxic and have a boiling point of 0–100 °C [11]. They are identified based on vapor pressures greater than 100 Pa and less than 1000 Pa and their ability to elute between n-hexane and n-hexadecane in a non-polar or

slightly polar gas chromatograph column [1,12]. VVOCs include propane, butane, methyl-chloride, methane, and acetylene from vegetation, soil, and microbial activity, volcanic emissions, the combustion of coal, refrigerants, landfills, and natural gas. Propane is the most toxic class of VVOCs, followed by butane, and then methyl chloride [2].

Table 1. Classification of volatile organic compounds.

Classes	Abbreviation	Example	Sources	Boiling Point	Reference
Very volatile organic compounds	VVOCs	Propane, butane, methyl-chloride, methane, and acetylene	Vegetation (isoprene and monoprene), soil and microbial activity (methane), volcanic emissions (methane and acetylene), combustion (propane, methane, ethane, and butane), refrigerants (chlorofluorocarbons), landfill gas (methane), natural gas (methane)	0 to 50–100	[1,2]
Volatile organic compounds	VOCs	Benzene (C6H6), formaldehyde (CH2O), toluene (C7H8), acetone (C3H6O), ethylbenzene (C8H10), chloroform (CHCL3), naphthalene (C10H8), trichloroethylene (C2HCL3), tetrachloroethylene (C2CL4) d-limonene, ethanol (ethyl alcohol), 2-proanol (isopropyl alcohol)	Benzene (gasoline), toluene (paint, thinner, adhesives), ethylbenzene (paint, ink), xylene (printing chemicals, rubber and leather industry), formaldehyde (building materials, preservatives, and household products, acetone (nail polish remover), naphthalene (mothballs), tetra chloroethylene degreasing agents, microbes	50–100 to 240–260	[1,13]
Semi-volatile organic compound	SVOC	Pesticides such as chloride and dichlorodiphenyl-trichloroethane (DDT), aldrin, dieldrin, plasticizers, e.g., phthalates, fire retardants, e.g., PCB-52,101,53, naphthalene, anthracene, benzo[a]pyrene and PBB, bisphenol A (BPA), nonylphenol	Pesticides, herbicides, burning of fossil fuels, volcanic eruption, carpets, flooring and wall covering), home care products (air freshener, perfumes, lotions, and shampoos)	240–260 to 380–400	[1,14]

VOCs, another class of volatile compounds, are emitted from a variety of compounds used in occupational settings. They are by-products of various chemical substances such as paint from the paint industry, as well as waxes and varnishes used in wood polishing [2]. They are atmospherically emitted in the form of benzene (C6H6), formaldehyde (CH2O), toluene (C7H8), acetone (C3H6O), ethylbenzene (C8H10), chloroform (CHCL3), naphthalene (C10H8), trichloroethylene (C2HCL3), tetrachloroethylene (C2CL4) d-limonene, ethanol (ethyl alcohol) 2-proanol (isopropyl alcohol) during various occupational activities [1]. VOCs are characterized with a boiling point range of 50–100 to 240–260 °C [1].

SVOCs are a class of organic compounds with a higher molecular weight than VOCs and VVOCs, as shown in Table 1. They have a boiling point range of 240–260 to 380–400 °C

and occurs in gaseous form and can be efficiently emitted into the atmospheric workplace because of their lower vapor pressure (10^{-9} to 10 Pa at a temperature of 25 °C) [15]. They mainly originate from organic agricultural products such as PCBs, polybrominated diphenyl ethers, phthalic acid esters, and PAHs [1,16].

Workers are exposed to VOCs through inhalation (via the lungs), absorption (via dermal contact), and ingestion (via the mouth). Inhaled atmospheric VOCs enter directly into blood circulation, unlike ingested VOCs that pass through the intestine to the liver and can be detoxified or entoxified. The effects of VOCs on workers can be monitored through the use of biomarkers, which are specific biological indicators that signify the level of exposure and susceptibility. Common biomarkers include exhaled breath analysis (benzene, toluene, ethylbenzene, and xylene), blood and urine (phenol (a metabolite of benzene) or hippuric acid (a metabolite of toluene)). Biomarkers remain invaluable tools for monitoring the rate of VOC exposure to workers' health [1]

VOCs interact with biological systems, including drug receptors, influencing the pharmacodynamics and pharmacokinetics of drugs (Table 2). For instance, chemical compounds containing substances such as propylene glycol (PG) and glycol ethers, formaldehyde, and benzene react actively with the component (mucin) in the mucous membrane of the epithelial lining of the respiratory system. This is because mucin is a polymer of glycoproteins, which is rich in amine groups. This amino end of mucin is nucleophilic, reacting with the C–O polar bonds in VOCs. The long-term exposure of an organism to VOCs results in a series of intramolecular reactions leading to the formation of a double-bonded C–N group, cross-linking with other similar compounds in the mucin. An antibody, immunoglobin E (IgE), detects these antigens (chemical reactions as a result of exposure) and triggers an inflammatory response [17].

Table 2. VOCs and receptor interaction in biological systems.

Example of VOCs	Target Receptor	Effects on Receptors
Benzene	Bone marrow	Hematotoxicity and immunotoxicity [17].
Toluene	Central nervous system receptors (GABA_A and NMDA)	Neurological effects. This interaction can modify the effects of drugs acting on these receptors, such as sedatives and anesthetics [17].
Formaldehyde	Cellular signaling pathways and glutathione receptors	Formation of adducts with DNA and proteins, affecting cellular signaling pathways and receptor functions. Inhibition of cellular detoxification processes and altering drug efficacy [17].

Figure 1 (VOC interaction pathway) shows that VOCs can bind to a receptor directly to mimic, activate or inhibit the binding of drugs. They can disrupt cellular functions and potentially affect human receptors such as the CNS, respiratory tract, and endocrine receptors responsible for drug metabolism and utilization. The binding of certain VOCs, such as benzene and toluene, can lead to receptor conformation, i.e., the modification of receptor sensitivity to the binding of drugs, and the activation or inhibition of enzymes such as cytochrome P450 and CYP2E1 responsible for drug metabolism. Enzymes play a critical role in converting dietary vitamin E (tocopherols and tocotrienols) into active forms that can provide antioxidant protection in the body. Also, the chronic exposure to VOCs such as formaldehyde can trigger oxidative stress and inflammation through the generation of ROS and inflammatory parameters [18].

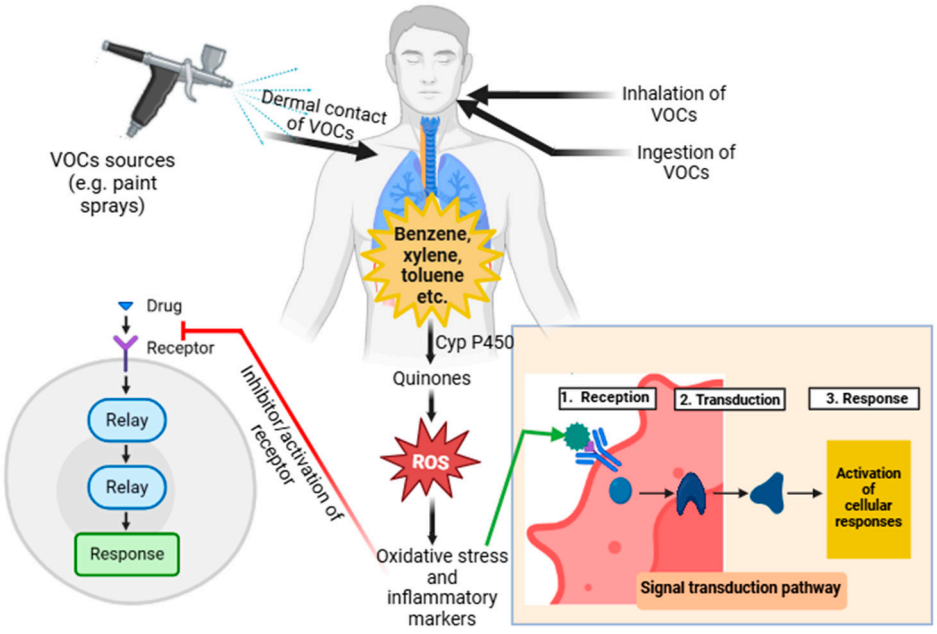


Figure 1. VOC–drug receptor interaction pathway.

2.1. Coal Tar Pitch: A Veritable Source of VOCs

Coal tar pitch, a by-product of coal processing, has many broad industrial applications, such as manufacturing aluminum, roofing, and paving [19]. When heated, it releases a complex mixture of VOCs, which are serious health hazards. The VOCs include polycyclic aromatic hydrocarbons (PAHs), benzene, toluene, and xylene, which are known to have high carcinogenic potency [20]. This raises a significant occupational health concern due to such toxic compounds in the workplace air, particularly in factories where coal tar pitch is heated to high temperatures [21].

Coal tar pitch compounds can bind to DNA, leading to cell mutation. This has been strongly associated with various cancer types [22]. For instance, the carcinogenicity of PAHs, especially benzo[a]pyrene, explains the lung cancer that is endemic in workers exposed to coal tar pitch fumes [23]. More prolonged exposure with poor respiratory protection increases the risk of lung cancer, especially in confined spaces [22]. Benzo[a]pyrene (BaP), a priority polycyclic aromatic hydrocarbon, also represents a principal constituent of coal tar pitch vapors and is a known animal carcinogen for the induction of lung and other cancers, including leukemia and lymphoma [24]. These are associated with the medication-induced suppression of normal bone marrow cell production and aberrations in leukocyte numbers responsible for night-fatal hematologic malignancies.

Skin exposure to VOCs from coal tar pitch has also been linked to an increased risk of skin cancers, particularly squamous cell carcinoma, in addition to cancers of the lung and blood [25]. The danger is heightened for workers with direct contact with the substance as the compounds can be absorbed through the skin. Another cancer common in these workers is bladder cancer, as PAHs are metabolized and excreted in urine [26].

VOC emissions from coal tar pitch also have environmental impacts, polluting the air, affecting communities, and leading to indirect health risks [27]. Regulatory standards exist but often do not go far enough to meaningfully reduce these risks. The findings suggest that in addition to tighter regulatory controls and continued investigation into safer handling practices in coal tar pitch-using industries, appropriate ventilation systems, effective monitoring, and the use of personal protective equipment are vital preventive measures.

2.2. VOCs Cause Chromosomal Aberration and DNA Damage

VOCs are recognized to influence chromosomal aberrations and noted to alter the DNA due to their reactive nature and through the generation of ROS. Different experimental investigations have revealed the genotoxic consequences of exposure to some particular VOCs using mammalian cells and genetic models to study the effects on chromosomes and DNA.

- Benzene Exposure and Chromosomal Aberrations

Benzene, a well-known industrial VOC, has been reported to be mutagenic [28]. Observations in laboratory test systems have revealed that benzene causes breaks and other forms of chromosomal aberrations in human lymphocytes, such as translocations and aneuploidy [29]. Metabolites of benzene, such as hydroquinone, produce ROS that led to DNA damage, affecting the structure of chromosomes. The micronucleus assay is also employed to compare the amount of chromosomal damage in benzene-exposed cells to an intact reference group, making it easy to see that benzene causes chromosomal instability [30].

- Formaldehyde is a known carcinogen that causes DNA damage in lung cells.

One of the common VOCs found indoors, formaldehyde, has been identified as producing DNA–protein crosslinks that impair DNA replication and repair [31]. Cells of human lung epithelial origin exposed to formaldehyde were found to have DNA strand breaks and chromosomal aberrations due to oxidative stress [32]. Comet assays, which measure DNA strand breaks, used in these studies reveal enhanced DNA fragmentation in cells exposed to formaldehyde [32].

- Acetaldehyde and genotoxicity in hepatocytes.

One VOC derived from alcohol metabolism, acetaldehyde, has been shown to be genotoxic and to precisely target hepatocytes [33]. In vitro experiments with cultured hepatocytes demonstrate that acetaldehyde treatments induce DNA adducts that can result in mutations and chromosomal rearrangements [33,34]. The enzymatic study detected the presence of acetaldehyde-induced DNA adducts attributed to mutagenesis and carcinogenesis, which are mainly seen in heavy drinkers [35].

These studies highlight the genotoxicity consequences of VOCs by using chromosomal aberrations and DNA damage induced by oxidative stress and direct interaction with DNA, which are essential for carcinogenicity risks and other pathology.

2.3. Some VOCs Are Mutagenic and Genotoxic

VOC mutagenicity and genotoxicity research has indicated that some VOCs cause mutations and DNA damage with consequences for health, including cancer. The following are some examples:

- Benzene and Genotoxicity In Bone Marrow Cells

Epidemiological and clinical data have shown that benzene—present in industrial emissions and gasoline—is a powerful genotoxin [36,37]. Research involving the use of mice and benzene shows that it causes changes in the bone marrow [38]. An enhanced micronuclei frequency in the exposed cells was also seen, a sign of chromosomal breaks and loss or even deletion [39,40]. This experimental evidence confirms benzene as a cause of leukemia in humans, especially due to chronic exposure.

- Formaldehyde's Mutagenicity in Human Nasal Epithelial Cells

Formaldehyde, now used in construction materials and consumer products, has been extensively investigated regarding its mutagenic properties [41]. Investigation on human

nasal epithelial cells using human subjects revealed that formaldehyde induces DNA–protein cross-linking and DNA strand-broken configurations [42]. These cells exhibited DNA fragmentation and oxidative stress using the comet assays. These studies further explain formaldehyde activity on upper respiratory tract cancers resulting from direct action on DNA and inhibitory effects on cellular DNA repair.

- The effects of toluene and DNA damage in mammalian liver cells

Toluene, a VOC present in paints, thinners, and adhesives, has documented evidence of damaging DNA in the hepatocytes [43]. These histological changes are accompanied by proof of toluene-induced DNA damage in rat hepatocytes in the form of increased tail intensity in comet assays and 8-oxo-deoxyguanosine, an oxidation product of DNA [44,45]. Toluene's metabolites are believed to produce ROS that can result in oxidative stress and possible mutagenic consequences, particularly when toluene exposure is sustained [46].

- Acetaldehyde is involved in the increased mutagenicity of gastrointestinal cells

Mutagenic effects on gastrointestinal tissues have also been linked to an intermediate product in the metabolism of alcohol known as acetaldehyde [47]. Earlier ex vivo studies on cultured human gastrointestinal cells have indicated that acetaldehyde, the final metabolite of ethanol, can bind with DNA and cause mutations during replication by forming adducts with guanine, among other bases [48]. In another scenario, an Ames test performed to evaluate mutagenicity showed that acetaldehyde possesses the ability to bring about mutations which are in agreement with the raised risk of gastrointestinal cancer among those people who consume alcohol heavily [48].

3. Drug Receptors

Drug receptors are particular macromolecules often found either on the cell's surface or intracellularly [1]. They are the direct objects on which drugs' actions are brought about. The involvement of a drug with its receptor triggers a cascade of chemical reactions that affect the organism's function [2]. Some of these receptors can be either attached to the cell membrane or present within the cytoplasm or even the nucleus, depending on the receptors' type and role [6].

When a VOC enters the body, it can either copy the effects of a substance naturally present in the body's system or inhibit it. It may also result in stimulating or preventing the enzymes from working, opening or closing the ion channels, influencing the cell's metabolism, or even altering gene expression [3]. The process of the VOC drug–receptor interaction obeys the mass action law, which states that the rate of a chemical reaction is directly proportional to the square root of the concentration of the reacting substances [1].

Hence, VOC–drug interaction receptors are essential to pharmacology since they aid in expounding or determining the actions of numerous drugs [4]. Knowledge about how VOCs engage drug receptors enables researchers and healthcare practitioners to anticipate drug outcomes, devise novel medications, and employ approaches to counteract unhealthy consequences. Receptors play a significant role in defining probably the three most important aspects of pharmacological operations of specificity, potency, and efficacy [6].

One of the positive parts of VOCs in receptor interaction and inducing a significant response in the drug targets is seen in VOCs from aromatic plants [5]. VOCs from aromatic plants are used for their therapeutic purposes because they are ingredients of essential oil, and essential oil can be described as a mixture of VOCs obtained from aromatic species such as bryophytes (liverworts) and higher plants through the aid of fractional distillation [6]. Plants' VOCs are characterized by low molar mass and low polarity expressed as lipophilicity (fat solubility). They have moderate polar heads composed of a keto or hydroxyl group that enables them to travel through the dermis and, therefore, can serve as

the penetration enhancer of drugs for target organs or receptor drug delivery [49]. Plant VOCs such as terpinene-4-ol or linalool used for drug delivery through encapsulation give more efficient transdermal penetration and absorption. VOCs used as drug delivery agents can influence the activity of cytochrome P450 enzymes and transferases involved in drug metabolism either by speeding or slowing down the metabolism rate or affecting the drug's half-life [50]. However, there is a great need for a comprehensive study of the type of plant VOCs that can be used as a delivery agent, as so many contain CYP isozyme inhibitors that increase peak plasma concentrations of the metabolite or change the rate of metabolism of specific components of the drug [51]. Therefore, the effect of the VOC–drug interaction could be additive, synergy, antagonist, or potentiator [52].

The interaction between a VOC's macromolecular constituents and the organism produces most of its effects. Through these interactions, the relevant component's functions may be changed, setting off a series of physiological and biochemical changes that typically affect the drug's reaction [53]. VOC–drug receptors, enzyme–substrate complexes, and antigen–antibody interactions share numerous characteristics. One of the most notable similarities between these interactions is the receptor specificity for a particular ligand. On the other hand, the receptor can link or transduce this binding into a response by inducing a conformational change or a metabolic effect, in addition to its capacity for identifying ligands [54]. VOC–drug receptors are proteins in cells; they cause biological reactions when a drug or endogenous chemical interacts with drug receptors. Drugs and ligands (VOCs) elicit cellular responses by binding to their respective receptors, which sets off a cascade of metabolic reactions. This process is called transduction of signals [55]. Many factors, such as the type of receptor, the VOC, the drug's affinity for the receptor, and the downstream signaling pathways that are triggered, affect the type and strength of the reaction.

4. Classifications of Receptors

Four primary families can be distinguished among drug receptors, the nuclear receptors, enzyme-linked receptors, ion channels, and G protein-coupled receptors (GPCRs) [56,57]. G protein-coupled receptors, or GPCRs, and ligand-gated ion channels, or LGICs, are two important protein families involved in membrane signaling that are also therapeutic targets [58]. The various classes of drug receptors that can be identified include the following.

4.1. G Protein-Coupled Receptors (GPCRs)

GPCRs are among one of the most significant and most diverse categories of receptors in the human body [56]. There are seven transmembrane helix-spanning receptors that are associated with guanine nucleotide-binding proteins (G proteins) [56]. Any time a ligand (drug, hormone, or VOCs) binds to the GPCR, it, in turn, activates or inhibits the G protein that sets off a sequence of intracellular signaling pathways. GPCRs contribute to many physiological functions, such as sensory perception, immune function, and neurotransmission. It includes adrenergic receptors that act on adrenaline and noradrenaline and the dopamine receptors [59].

4.2. Ligand-Gated Ion Channels

Another significant and diverse type of receptor is the ligand-gated ion channels [7]. These are ion-gated local anesthetic-affected membrane SSFs that open or close on contact with a chemical messenger (ligand). Opening these channels lets ions like sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), or chloride (Cl^-) cross the membrane and cause variations in cell membrane potential and cell functions [7]. Some prime examples include the nicotinic acetylcholine receptor, which triggers muscle contraction, and the gamma-aminobutyric

acid (GABA) receptor, which is essential for the inhibitory transmission of the central nervous system. In the neurological system and skeletal neuromuscular junctions, LGICs are transmembrane proteins controlling the passive passage of specific ions across cell membranes. Neurotransmitter binding to orthosteric sites causes conformational changes in the LGIC, which open the ion channel's "gate" and increase ion conductance [60,61]. The transmembrane pore allows ions to temporarily pass through when an external ligand is bound, which is the characteristic of ligand-gated ion channels. Purinoreceptors, glutamate receptors, and Cys-loop receptors are the three superfamilies into which ligand-gated ion channels are generally subdivided. The different topographical morphologies of the receptors, which in turn provide functional distinctions, are the basis for this division. Due to their variable expression in space and time, ligand-gated ion channels are linked to several important cellular functions [60]. Conventionally, LGICs are categorized into two types of ion channels, the anion-selective, which includes the inhibitory type A γ-aminobutyric acid (GABAA) and glycine (Gly) receptors, and the cation-selective, which provides for excitatory P2X, serotonin type 3 (5-HT3), nicotinic acetylcholine (nACh), N-methyl-D-aspartate acid (NMDA), and α-amino-3-hydroxy-5-methyl-4-isoxazole-proprionic acid (AMPA) receptors. These receptors, engaged in various pharmacological and pathophysiological activities, are homomeric or heteromeric assemblies of homologous subunits [62].

4.3. Tyrosine Kinase-Linked Receptors

These receptors are transmembrane proteins, and their intracellular domain possesses tyrosine kinase activity [8]. When the ligand binds to the extracellular domain, this results in conformation change, dimerization, and autophosphorylation of the receptor that activates the kinase domain. This activation triggers a series of signals in the downstream path that results in different cellular actions like growth, differentiation, and metabolism. Some examples are insulin receptors and epidermal growth factor receptors (EGFR) [6].

4.4. Intracellular Receptors

This type of receptor is almost always located inside the cell, either in the cytoplasm or in the nucleus. These receptors interact primarily with lipophilic substances that can enter the cell through the membrane. On binding to a ligand, many of these receptors act as transcription factors, becoming involved in the control of gene transcription. Steroid hormone receptors are examples of nuclear receptors, such as the glucocorticoid and thyroid hormone receptors [6].

5. Roles of Receptor in VOC–Drug Interactions

5.1. Receptor Selectivity

Receptor selectivity can be defined as the ability of a ligand (drug/VOC) to interact with a particular receptor type or its subtype more adequately compared to other receptor types [62]. High selectivity is sometimes considered ideal for drug development because its use results in a precise therapy and lesser chances of producing toxicological outcomes. For example, atenolol is a drug that is selective for beta-1 adrenergic receptors of the heart to avoid its action on beta-2 receptors in the lungs, thus decreasing the pre-multiplied break in asthmatic patients. Still, certain VOCs in the same receptor can inhibit or slow the drug's action [59].

5.2. Receptor Affinity

Receptor affinity refers to measuring the intensity of the drug/VOC–receptor interaction. High-affinity drugs, or VOCs, attach and interact more strongly with their targets. They are usually active at lower concentrations, which may increase their strength and re-

quire less amount to be taken [59]. However, exorbitant receptor affinity can again threaten receptor occupancy for a long time in the presence of VOCs, and the receptor can become desensitized or downregulated, which will reduce the drug's efficacy in the long run. The proportioning of affinity is significant for obtaining the best therapeutic results without compromising tolerance or resistance receptors [56].

5.3. Efficacy and Safety

The therapeutic effect of a drug depends on the drug's ability to interact with a target structure and activate it to produce a therapeutic effect. Drugs more selective with the correct receptor affinity will not interact with other receptors, possibly causing off-target effects, but will only stimulate the required effects [63]. Safety is also a significant factor; any compound that may be non-selective or may have an affinity for the wrong receptor is likely to exert its effects on other receptor sites, and thereby result in high side effects and toxicity profiles [63]. Therefore, receptor selectivity and affinity are the keys to making novel pharmacological agents therapeutic and without side effects. Thus, new medications have been developed that increase the potency and effectiveness of the treatment or reduce undesired side effects from the interaction with incorrect receptors or other undesirable binding properties, which, in turn, optimizes the patients' treatment [57].

6. Computational Modeling Technique for Stimulating VOC–Drug Receptor Interactions

6.1. Molecular Docking

Molecular docking is one of drug design's most widely used computational modeling techniques. It involves predicting the preferred orientation of a drug molecule when bound to a target protein, which helps in understanding the binding affinity and activity of the drug [64]. Docking algorithms, such as AutoDock and Glide, simulate the interaction between ligands and receptors and can provide insights into the molecular basis of VOC–drug efficacy. The recent advances in docking methodologies can improve accuracy and efficiency, enabling the identification of potential VOC–drug candidates with a higher precision [65]. Quantitative structure–activity relationship modelling is also a computational approach that correlates the chemical structure of compounds with their biological activity. Using statistical methods, QSAR models predict the activity of new compounds based on their structural attributes [66]. This technique is beneficial in lead optimization, where modifications to chemical structures are made to enhance drug potency and reduce toxicity. Recent studies have integrated machine learning algorithms with QSAR models, producing more robust and predictive models [67]. Molecular dynamics simulations provide a dynamic view of molecular interactions, offering insights into the behavior of VOC molecules and their targets over time. By simulating the physical movements of atoms and molecules, MD can help understand the stability, conformational changes, and binding kinetics of the effect of VOCs on drug–target complexes [68]. The advances in computational power and algorithm development have made MD simulations more accessible, allowing for studying complex biological systems at an atomic level [69]. Pharmacophore modelling identifies the spatial arrangement of features necessary for a ligand to interact with its target. A pharmacophore is a three-dimensional arrangement of functional groups essential for biological activity [69]. This technique is instrumental in virtual screening, where databases of chemical compounds are screened to identify those that match the pharmacophore model. The recent improvements in pharmacophore modelling, such as machine learning and AI integration, have enhanced the accuracy of virtual screening processes [70]. Homology modelling, also known as comparative modelling, predicts the three-dimensional structure of a protein based on its sequence similarity to a known structure (template). This

technique is crucial for studying proteins without experimentally determined structures. Through the alignment of the target protein sequence with the template, homology modelling generates a model that can be used for drug design and docking studies [71]. Recent advances in template selection and alignment algorithms have improved the reliability of homology models [72].

6.2. Structural-Activity Relationship Studies

SAR studies have evolved significantly since their inception in the early 20th century. Initially, SAR analyses were largely empirical, relying on trial-and-error methods to identify active compounds. However, with the advent of computational chemistry and molecular modelling, SAR has become more systematic and predictive [73]. Modern SAR studies utilize various computational tools, including quantitative structure–activity relationship (QSAR) models, molecular docking, and machine learning algorithms, to predict the biological activity of novel compounds based on their chemical structure [74].

Recent advances in computational techniques have significantly enhanced SAR studies' predictive power and efficiency. Machine learning and artificial intelligence (AI) have emerged as powerful tools in SAR analysis, enabling the processing of large datasets and the identification of complex patterns that might be missed by traditional methods [75]. Deep learning, in particular, has shown promise in improving the accuracy of QSAR models by capturing intricate relationships between molecular structures and biological activities [76].

Additionally, integrating cheminformatics with bioinformatics has facilitated the development of more comprehensive SAR models. These models consider the chemical properties of compounds and their interactions with biological targets, such as proteins and enzymes [77]. This holistic approach has proven effective in identifying potential drug candidates with high specificity and efficacy. SAR studies play a crucial role in the early stages of drug discovery. Researchers can design analogues with improved potency and selectivity by elucidating the structural features that contribute to a compound's biological activity. For instance, SAR analysis has been instrumental in developing kinase inhibitors for cancer treatment. Through the examination of the interactions between kinase enzymes and various inhibitors, researchers have been able to design compounds that selectively target specific kinases implicated in cancer progression [77].

Another notable application of SAR is in the design of antimicrobial agents. With the rise in antibiotic resistance, there is an urgent need for novel antibiotics with unique mechanisms of action. SAR studies have helped identify structural motifs that enhance the antibacterial activity of compounds while reducing their susceptibility to resistance mechanisms [77].

6.3. Computational VOC Ligand–Receptor Interactions

The VOC ligand–receptor interaction studies using experimental and computational approaches have accelerated the understanding of ligand–receptor interactions of a few VOCs with their biological targets, which are needed for effective environmental and therapeutic research.

- Olfactory receptor-ligand binding

Molecular docking and molecular dynamics simulations are computational approaches particularly useful for studying olfactory receptors (ORs) and their interactions with VOC ligands [78]. ORs are G-protein-coupled receptors (GPCRs) that sense a wide range of volatile organic compounds (VOCs) and are thus essential for the sense of smell [79]. Due to the ability of some plant volatile organic compounds (VOCs) to bind to receptors, the characterization of ligand-binding predictions in silico can model binding specificity and

affinity profiles of different ligands [80]. Such models simulate ligand binding on an atomic level and can localize binding sites, calculate interaction energies, and even predict conformational flexibility in ORs upon ligand binding. In the next step, molecular dynamics simulations would complement the determination of the stability of these ligand–receptor complexes over time, helping to better understand the binding dynamics and specificity. Often, it is followed by the experimental confirmation of such predictions using fluorescent markers or calcium imaging in cell culture where OR activation is immediately observed, demonstrating computational predictions of OR function [80].

Research has validated the VOC–receptor interactions predicted by their computational model using heterologous expression systems such as HEK293 cells [81]. In one example, real-time receptor activation measurements using highly sensitive cellular biosensors have demonstrated interactions with hexanol and isovalent acid; the studies have shown both receptor sensitivity and ligand specificity [82].

- Plant VOC and Insect Olfactory Receptor Studies

Olfactory cues to locate host or food sources are heavily relied upon by many insects, especially female mosquitoes, as well as many agricultural pests like fruit flies (mediated by their antennae). Plant volatile organic compounds (VOCs) also serve as chemical signals to attract or repel insect herbivores or their predators [81]. Computational studies on insect olfactory receptors (ORs) can indicate the binding manner of these plant VOCs [83,84]. Computational modelling also provides insights into the active site of a receptor, predicting whether the bound ligand will activate or inhibit the receptor [85]. That information makes it useful for applications, such as compounds that deter and disrupt host-finding. Plant-derived compounds such as linalool and citronellal, active on ORs in mosquitoes, have experimental evidence supporting their repellent potential [86].

Electrophysiology and behavioral assays that strengthen computational findings of VOC–insect olfactory receptor interactions are standard features of experimental studies [87]. In release studies with live mosquitoes, attraction or repellency to synthetic VOCs predicted to bind to receptors have been applied, such as linalool and eugenol [88].

- Human Pathogen Detection

Volatile organic compounds (VOCs) are non-invasive biomarkers for diseases that can be detected in human breath or other emissions [89]. Various studies have shown how a few VOCs are linked to the development of diseases (i.e., lung cancer and gastrointestinal diseases) [90]. The prediction of VOC–receptor binding affinities using machine learning models along with molecular docking can allow the engineered synthetic receptor to mimic the biological system in such a way. For example, the binding potential of VOCs associated with elevated breath acetone in diabetics is also analyzed on synthetic receptors [90].

7. High-Throughput Screening Methods

HTS involves using automated robotic systems, sensitive detectors, and data processing software to conduct experiments on a massive scale. The primary goal of HTS is to quickly identify active compounds, antibodies, or genes that modulate specific biological pathways. Key technologies employed in HTS include microplate readers, liquid handling systems, and various assay formats such as fluorescence, luminescence, and absorbance-based assays [91].

Microplates, typically 96-, 384-, or 1536-well plates, are essential for HTS, allowing the simultaneous testing of multiple samples. Robotic liquid handlers ensure precise dispensing of reagents, reducing variability and increasing reproducibility [92].

Recent advances in HTS technologies have significantly improved the efficiency and accuracy of screenings. Miniaturization of assays has enabled the use of smaller sample

volumes, reduced costs, and increased throughput [91]. Additionally, the development of label-free detection methods, such as surface plasmon resonance (SPR) and mass spectrometry, has provided new avenues for studying biomolecular interactions without the need for fluorescent or radioactive labels [93].

Integrating artificial intelligence (AI) and machine learning (ML) into HTS has also revolutionized data analysis. AI and ML algorithms can process vast amounts of data, identify patterns, and predict the biological activity of compounds, thereby accelerating the drug discovery process [94]. HTS is widely used in drug discovery to identify potential therapeutic candidates. By screening large compound libraries, researchers can quickly pinpoint molecules that exhibit desired biological activities, such as enzyme inhibition or receptor binding [95]. HTS has been instrumental in identifying lead compounds for various diseases, including cancer, infectious diseases, and neurological disorders.

In genomics, HTS methods, such as CRISPR-Cas9 screening, have facilitated the identification of gene functions and interactions. These screenings help elucidate genetic pathways and identify potential targets for genetic therapies [96]. Additionally, HTS is employed in functional genomics to study the effects of gene knockdowns or overexpression on cellular phenotypes [96].

HTS has also found applications in environmental science, where it is used to screen for chemicals' toxicological effects on various biological systems. This approach helps assess pollutants' environmental impact and develop strategies for bioremediation [97].

8. Fragment-Based Drug Design

Fragment-based drug design involves the identification of small chemical fragments, typically with molecular weights less than 300 Da, which bind to a target protein with low affinity [98]. These fragments are optimized through structure-based design to improve their binding affinity and specificity. The process typically involves fragment screening, identification of binding sites, and iterative optimization cycles [98].

One of FBDD's primary advantages is its ability to explore a more extensive chemical space with fewer compounds than traditional high-throughput screening. This is because fragments are smaller and can sample diverse regions of chemical space more efficiently [99]. Additionally, FBDD allows for identifying novel binding sites and mechanisms of action that may not be apparent through other methods [100]. The smaller size of fragments also makes them more likely to achieve high binding efficiencies, a critical factor in drug development.

Several biophysical techniques are employed in FBDD to detect and characterize fragment binding. These include nuclear magnetic resonance (NMR) spectroscopy, X-ray crystallography, surface plasmon resonance (SPR), and isothermal titration calorimetry (ITC) [101,102]. NMR spectroscopy and X-ray crystallography are particularly valuable for providing detailed structural information about fragment binding, which is crucial for subsequent optimization [101].

FBDD has led to the discovery of several successful drug candidates and approved drugs. One notable example is Vemurafenib, a BRAF inhibitor used to treat melanoma. The discovery process involved the identification of a fragment that bound to the ATP-binding site of BRAF, which was subsequently optimized to produce Vemurafenib [103]. Another success story is Venetoclax, a BCL-2 inhibitor used to treat chronic lymphocytic leukemia. Venetoclax was developed through the optimization of a fragment that bound to the BH3 binding groove of BCL-2 [104].

9. Molecular Dynamics (MD) Simulations

Molecular dynamics simulations afford lengthier and more detailed time scales of the dynamics of drug–receptor binding. This technique mimics the motion of atoms and molecules; thus, researchers can study a drug's interaction with its target under physiological conditions. It became clear from these MD simulations that important information about the stability and flexibility of the drug–receptor complex and potential conformational changes affecting the binding affinity of the efficacy of a drug could be obtained [101].

10. Modulatory Receptor Activity Role

10.1. Allosteric Modulation

Allosteric regulation implies altering a receptor's function by molecules bound to receptor sites different from the orthosteric site where endogenous ligands typically interact. Positive or negative allosteric modulators act as either positive or negative regulators of the receptors. This strategy holds several advantages, including high selectivity and the absence of side effects, as allosteric modulators more often than not amplify, rather than completely inhibit or stimulate, the receptor's function. For instance, benzodiazepines are positive allosteric modulators of the GABA_A receptor that strengthen the still inhibitory function of GABA and render anxiolytic and sedative effects [56].

10.2. Competition for Binding Sites

Competitive inhibition happens when a drug directly competes with the endogenous ligand to interact with the orthosteric site of the receptor. Such an interaction is either reversible or irreversible. Like most other enzyme inhibitors, the reversible competitive inhibitors attach loosely to the enzyme's active site. They can easily be detached by the upsurge in the concentration of the enzyme's regular substrate. The irreversible inhibitors, in contrast, attach to the receptor by coordinating a covalent bond with it, meaning that the receptor is permanently inactive. They are usually employed to prevent specific signaling pathways from 'going haywire'. For instance, beta-blockers act in a way that inhibits catecholamine from combining with the beta-adrenergic receptors, hence lowering heart rate and blood pressure in hypertensive patients [104].

11. Regulatory Hurdles in Drug Approval for Occupational Exposure

The approval procedures for drugs used in occupational exposure consist of several stages and criteria of high standards for protecting employees exposed to different hazards at the workplace. These multiple steps for the regulatory challenges include the following:

Extensive Preclinical Testing: A system of preliminary studies is essential to assess the toxic effects of a drug in animals before administrating it to human beings. Such investigations help determine the possible risks and set maximum and minimum exposure levels [105]. Knowing the action of a medicine in the human body requires researching how it works in the body concerning its modes of action, absorption, distribution, metabolism, and excretion (ADME).

Clinical Trials: These come in different stages I–III, as follows:

- Phase I Trials: These are the first to assess the safety, tolerability, absorption, distribution metabolism, and excretion of a drug with fewer healthy volunteers or subjects exposed to workplace hazards [106].
- Phase II Trials: Next, associated clinical studies are carried out to evaluate safety and efficacy in an even larger population of people exposed to or prone to occupational exposure.

- Phase III trials are large-scale research studies conducted to confirm drug effectiveness, observe undesirable effects, and collect data essential for the medication's usage at the workplace [107].

Specific Regulatory Requirements: Such requirements ensure that the medications do not expose the employees to even higher risks. Studies about the drug's environmental impacts, especially in places of work that dispose of the compounds chemically, are carried out [108].

Post-Market Surveillance: After the medication has been approved and taken in a workplace, there should always be a checkup to ensure the side effects that may occur. To monitor and, where necessary, evaluate the extent of the injuries resulting from drug use, the reporting of these is commonly required. This includes daily assessments of the efficacy and risk profile of the drug in the workplace to confirm compliance with the legal provisions at constant intervals [109].

Labelling and Documentation: Health-related authorities demand more elaborate labelling, which has to contain information on safe use, possible side effects, and definite guidelines for workers [67,110]. This ranges from Material Safety Data Sheets (MSDSs) concerning the use of chemicals to ensure that the employer and employees have sufficient education on the drug's use, the risks, and the effects of untoward incidents.

Ethical Considerations: Employers who volunteer to participate in clinical trials must do so voluntarily and knowing the drug's consequences and/or outcomes. A detailed assessment must be made to ensure that the drug's positive impact will reciprocate the probable danger it will pose to the workers [111].

Interagency Coordination: Collaboration between several governmental institutions, like the FDA and OSHA in the USA, to synchronize the rules and regulations for medicines administered in occupational situations [112].

Compliance with International Standards: Entities in the international supply chain and MNEs must adhere to the WHO and ILO regulations preventing the use of lower-quality or substandard products for exports to global markets [113,114].

12. Emerging Technological Trends

Artificial intelligence and Machine learning: New advances in AI and ML have impacted a number of the aspects of computational drug design in the recent past [57]. Such technologies can mine big data to provide concrete information and forecast how some of the chemicals called VOCs react with drug receptors [115]. AI and ML are helpful in the operations that enhance lead compounds, estimating the ADME properties, and always cutting down on the time and costs of drug development [116]. Of the various heads of ML, deep learning is tremendously valuable for learning the intricate patterns relating to chemical structures and biological activities, making it possible to develop better and more selective drugs [117].

Molecular Dynamics Simulations: Molecular dynamics (MD) simulations give information regarding the change in VOC–drug receptor interactions with time [118]. Since its inception, enhancements have been made to the computational power and the algorithms used for MD simulations, making them more accurate and easier to perform [119,120]. Such simulations can follow the motion of atoms and molecules and explain how exactly VOCs interact with receptors under physiological conditions [121]. For this reason, this information is paramount for understanding aspects such as binding affinity, conformational changes in the receptor, and off-target interactions that need to be considered for designing safer and more effective drugs.

12.1. Quantum Mechanics/Molecular Mechanics (QMs/MMs)

This hybrid style of modelling chemical systems uses quantum mechanics for the neighborhood of the molecular region of interest and classical mechanics outside the area [122]. The combination of QMs/MMs has improved the computational models in drug design because of the accuracy of the two methods [123]. Thus, QMs/MMs approaches are employed to increase QMs' accuracy in modelling electronic structures with MMs' efficiency in handling large biomolecular systems [124]. This hybrid approach is most beneficial in analyzing VOC–drug receptor interactions; it provides information on the electronic and steric characteristics of binding specificity and affinity [125].

12.2. Combination of Multi-Omics Strategies in VOC–Drug Receptor Interaction Research

Genomics: Diagnostic methods like NGS enable the comprehensive assessment of genetic factors determining a person's susceptibility to VOCs and medication response [126]. Thus, genetic polymorphisms and mutations in drug receptor genes are targets for researchers to develop individual therapeutic interventions, considering the differences in vulnerability to VOCs and the effectiveness of treatments [127]. Reflected on such deliverables, genomic data may also provide new drug targets and genetic pathways associated with VOC detoxification and metabolism [128].

Transcriptomics: This focuses on the changes in gene expression in VOC-exposed cells and cells treated with drugs. mRNA levels that RNA sequencing (RNA-seq) technologies can quantify offer information on the VOC-impacted regulatory networks and signaling pathways [129]. This information is relevant for decoding the toxicity of VOCs and finding markers of exposure and the effectiveness of therapeutic interventions. Combining the data obtained from transcriptomics with the data from drug receptor research improves the definition of the target pathways for treating pathological processes.

Proteomics: Proteomics can be described as a large-scale approach for proteins involving their synthesis, post-translational modifications, or interconnectivity [130]. Proteomic approaches in MS can determine and compare the expression of proteins vulnerable to VOC impact, thus illustrating alterations in signal transduction and metabolic pathways [131]. The proteomic data can also reveal the effect of the drug and its targets as well as off-target effects, which helps in developing a more selective and efficient drug [131]. With the help of proteomic data together with genomic and transcriptomic information, molecular processes of VOC–drug receptor interactions could be explained in more detail.

Metabolomics: Metabolomics is all about studying small metabolites within biological systems in the form of a specimen [132]. This approach offers an understanding of metabolism alterations resulting from the impact of VOCs and drug treatment [133]. Thus, metabolomic profiling can discover biomarkers concerning VOC toxicity and treatment efficacy, which will be helpful for the creation of new drugs that target particular VOC-induced metabolic pathways of detoxification and repair [134]. Combining metabolomic data with other omics technologies helps to comprehend the biological impact of VOCs and their modulation by drugs.

12.3. Targeting Specific Biological Pathways for VOC Detoxification

The methods described below are concerned with the process of VOC detoxification.

12.4. Cytochrome P450 Enzymes

The CYP system is regarded as the most important in vitro enzymatic model for studying VOC metabolism and detoxification [135,136]. Thus, it can be understood that the selective modulation of particular CYP enzymes involved in the metabolism of VOCs can improve the detoxification process and decrease toxicity. For instance, developing drugs

that activate or inhibit specific CYP isoforms helps alter the metabolic pathways of VOCs and, hence, the extent of toxicity. Further, the genetic polymorphism of CYP enzymes' identification can assist in choosing individual approaches to therapeutic actions, which will cause maximal detoxification and minimal side effects.

12.5. Glutathione Pathway

The glutathione (GSH) pathway is one of the most important antioxidant processes that rules the neutralization of reactive oxygen species (ROS) and the metabolites of elective VOCs [137]. The activity of enzymes associated explicitly with GSH synthesis and conjugation, like GSTs, can increase VOC detoxification [138]. Drugs that raise intracellular GSH levels or have GSH-like effects can protect against VOC-induced oxidative stress and toxicity [138]. Searching for molecules with similar activity to the natural compounds of the GSH pathway in the human body and, thus, finding synthetic analogues is a practical approach for developing VOC detoxification therapies.

12.6. Antioxidant Defense Mechanisms

Some VOCs produce ROS that cause oxidative stress, cell damage, and toxicity. The antioxidant protection systems are aimed at reducing the VOC-elicited oxidative damage and increasing the cellular protection capability [139]. Pharmacological agents that enhance the Nrf2 pathway, which is a master switch in antioxidant response, might increase the levels of antioxidant enzymes and protective proteins [140]. Hence, creating compounds that can neutralize ROS through direct reaction or by raising the body's internal antioxidant defenses can also lower VOC toxicity and enhance the quality of life.

12.7. Inflammatory Pathways

Bioactivation can provoke inflammatory reactions in cells that receive VOCs and, therefore, plays a role in their toxicities. Some authors have shown that antagonizing specific mediators of inflammation would help prevent inflammation and tissue damage due to VOCs [141,142]. For example, drugs being worked on as NF-κB signaling inhibitors help reduce the production of cytokines and mediators of inflammation. Furthermore, drugs that can reduce the activity of cyclooxygenase enzymes and other mediators of inflammation can help manage VOC-induced inflammation and treatment outcomes [143].

12.8. Collaborative Efforts and Interdisciplinary Research Initiatives

Academia–Industry Partnerships: Therefore, there is a need for combined efforts between academic institutions and the pharmaceutical industries in the enhancement of VOC–drug receptor interaction. Academia offers scientific concepts, new ideas, and medicine, whereas industry offers assets, know-how, and facilities for the production of drugs. These collaborations may make applying basic research results to therapeutic applications easier, in this case, by increasing the pace of identifying and developing drugs against VOC-mediated toxicity.

Government and Regulatory Agencies: Universities, ministries of health, and pharmaceutical regulators are at the forefront of supporting research and guaranteeing the safety and effectiveness of new drugs aimed at VOC exposure. Students and researchers who apply for funding programs, grants, and professional guidelines may encourage the investigation of VOC drug receptors and the formulation of secure and innovative treatments. Relations with regulatory bodies can also help facilitate the approval of new products, which would be beneficial in providing proper access to innovative products for the population exposed to VOCs.

Interdisciplinary Research Teams: To tackle VOC–compound receptor interaction problems, dynamic and multifaceted projects are needed, whose objectives involve infor-

mation exchange between chemists, biologists, toxicologists, pharmacologists, and data scientists. These teams may encompass various specializations and experiences and, hence, can encourage creative solutions. International cooperation should help apply the new computational models for gene expression analysis and implement multi-omics strategies and high-throughput screenings to find new targets for VOC detoxification and develop effective treatments.

Global Health Initiatives: Global health promotion programs targeting people and communities' environments and workplace health can help ignite research on VOC exposure and inform policies. International collaborations and partnerships enhance the exchange in information and working models, thus assisting in establishing international strategies for detoxification and clearance of VOCs [144]. They may also increase people's knowledge regarding the adverse health effects of VOCs and lobby for more effective legislation and safeguards in employment areas and environments.

Personalized Medicine: Due to the combination of omics technologies and computational strategies, it has been possible to develop approaches towards personalized medicine to manage VOC detoxification. Employing each person's genetic, transcriptomic, proteomic, and metabolomic data, the researchers can design specific treatment plans to consider the subject's vulnerability to VOC and response to therapy. It is concluded that 'tailored' treatments in the context of VOC detoxification could improve the effectiveness and safety of health interventions for people exposed to VOCs [145].

Natural Products and Biologics: The talk on natural products and biologics provides fresh approaches to VOC purification [145]. Challenged with corruption, natural substances obtained from plants, microorganisms, or marine organisms may offer unique features that facilitate detoxification and shield them from VOC toxicity. Antibodies and peptides associated with VOC metabolism and detoxification can be potentially used in biophysical targeting. Scientific studies on natural products and biologics can identify new drugs with unique mechanisms of action that are helpful in VOC removal [146].

13. General Environment and Auditing: Monitoring and Risk Evaluation

Enhancements in environmental monitoring methods can enhance the identification and quantification of the presence of VOCs in workplaces and contaminated environments [147]. Techniques like real-time monitor systems, wearable sensor devices, and biomonitoring can give real-time information about the extent of VOCs and exposure [148]. Combining VOC–drug receptor interaction studies with environmental monitoring can help assess risk and identify timely interventions to reduce VOC exposure and toxicity [149].

Sustainable and Green Chemistry: It is possible to influence such a state of affairs by applying sustainable and green chemistry principles in the drug synthesis and production stages. Green chemistry, therefore, involves avoiding the use of hazardous substances and waste and optimizing resource usage [150]. Through the realization of innovative green processes and green materials, experts can devise ways of minimizing the concentrations of VOCs and hence promote better occupational and environmental health [151].

In conclusion, understanding the interactions between VOCs and drug receptors can be the basis of the search for ways to prevent the toxic effects of VOCs that are dangerous for people's health [152]. Progress in computational drug design and molecular modelling, systems bioinformatics, pathway and network targeting, synergy-based research, and current trends, including personalized medicine and green chemistry, are the trends in the future of the field. In this regard, the following strategies can be followed by researchers to obtain new drug targets, develop more effective and less toxic treatment options, and respond to increasing occupational health problems related to exposure to VOCs.

13.1. Challenges

The challenges are associated with utilizing the VOC–receptor interactions for drug design (e.g., identifying specific VOCs and their target receptors, attending to safety considerations) [153] Also, one of the key difficulties to overcome while employing the reinforcement VOC–receptor interfaces as templates for drug development is the recognition of which VOCs and their reacting receptors are most appropriate. VOCs include a large variety of chemical species with different structures and affinities; therefore, it becomes problematic to identify which are relevant to occupational exposure and toxicity. Furthermore, it is essential to determine the target receptors for these VOCs, which also need a lot of effort and highly analytical methods [154]. This process often takes time and consumes many resources, such as high-throughput screening, computational modelling, and experimental validation which are used to prove the VOC–receptor interaction.

13.2. Complexity of VOC Mixtures

VOCs are mainly identified in occupational environments where people are exposed not only to single VOCs but also to their combinations [155]. These mixtures sometimes interact in synergy, additively or even antagonistically, thus making it hard to analyze VOC–receptor interactions. It is difficult to comprehend the additive, synergistic, or antagonistic impact of more than one VOC on the activity of the receptor and its resulting cellular consequences. For this reason, researchers must employ advanced models and experimental systems to understand the mechanisms in VOC mixtures and their effects on biological systems.

13.3. Variability in Individual Responses

This is included because people have different susceptibilities to fatigue, and similarly, they differ in their response to exposure to VOCs. Also, one can distinguish genetic polymorphisms, epigenetic modifications, and differences in metabolic rates, which determine the course of VOC metabolic processes and responses [156]. This variability poses a challenge in developing the general biomarkers and targets of VOC toxicity [157]. Solutions considering the population's internal variety are necessary to find and establish valid treatments. However, obtaining data on the standard and differential AI genomics and metabolism information is not always possible.

13.4. Safety Considerations

Concerns of safety are highly sensitive when it comes to drugs that influence the VOC receptors. Many VOCs can act toxicologically at very low levels, and therefore, the drug's interaction with VOCs or its metabolites should be studied to prevent any negative consequences [156]. However, safe drug design targeted at modulating VOC–receptor interactions should incorporate the safety assessment of these drugs while they are in the process of long-term preclinical and clinical development. Therefore, these drugs' safety and efficacy should be regulated and upheld to the highest safety standards.

13.5. Technological and Methodological Limitations

Technological and methodological issues limit the analysis of the relationship between VOCs and receptors [158]. Today's analytical methods may not be sensitive and specific enough to identify trace amounts of VOCs and their metabolites in biological fluids [159]. Also, current computational models might not capture the biomolecular interactions between VOCs and receptors in a proper manner, which calls for futuristic algorithmic and simulation approaches [160]. Therefore, the ability to overcome such limitations is crucial in the identification of VOCs and their receptors for the development of drugs. Further re-

search is still required on the mechanisms of ultra-low temperature and clinical applications of the technique.

13.6. Mechanistic Studies

More studies have to be conducted on the molecular level to determine how VOCs bind to specific receptors and what consequences these can have. Thus, mechanistic animal studies should include determining the molecular targets and signaling pathways that are impaired or modulated due to VOC exposure and receptor activation. For this reason, understanding these mechanisms is central to the development of effective drugs to treat VOC-induced toxicity and its negative impact. Further studies should also focus on identifying downstream cell signaling pathways of VOC–receptor interactions, including the secondary messengers, transcription factors, and epigenetic modulators [161].

13.7. Biomarker Discovery

Therefore, elucidating specific VOC biomarkers that can be used for exposure assessment and evaluating toxicity severity in worker populations is crucial for occupational health and in assessing the efficacy of the therapies. VOC current biomarkers can include exposure, efficacy of VOCs, and information on treatment results. Further research has to determine specific biomarkers that are sensitive enough and that can be easily measured in clinical practice. Omics technologies related to genomics, proteomics, and metabolomics will, to some extent, help discover new biomarkers or provide a deeper insight into the biological effects provoked by VOCs [114].

13.8. Clinical Trials and Applications

From this information, it is easy to determine that converting the literature findings about VOC–receptor interactions into clinical practice involves conducting clinical studies to assess the effectiveness and safety of potential treatments. These trials should be conducted on various population types and account for the variations in VOC metabolism and the related response. Moreover, further research conducted in clinical trials should contain the idea of the use of drugs that work through similar paths affected by VOCs. All these stakeholders must work together to incorporate research findings into practice targets.

13.9. Preventive Strategies

Besides treatment, efforts should be made to identify methods for environmental controls that prevent the occurrence of VOCs and their effects on the human body. This concerns the evaluation of a protective measure of efficiency and effectiveness, such as the PPEs, engineering control, or environmental check. Measures that should be taken to reduce exposure to VOCs and enhance occupational health should also be developed and implemented in public health programs and workplace policies. Combining the preventative measures and the therapeutic interventions can go a long way towards offering an extensive strategy for combating the VOC effects on health.

13.10. Interdisciplinary Collaboration

As seen from the discussions on the challenges concerning the relationships between VOC receptors and their uses in drug development, a multidisciplinary approach is needed. Joint efforts of scholars in chemistry, biology, toxicology, pharmacology, and environmental health should enhance understanding of the malevolent effects of VOCs and elaborate on prevention strategies. Such a synergy of disciplines allows for the best utilization of resources and increases the rates of scientific advancement and research [162].

14. Cancer and Cancer Drug Resistance; Role of Big Data in Enhancing Disease Treatment

Cancer is still a leading cause of death across the world and is evidenced by the uncontrollable division of cells that are morphologically and functionally distinct [163]. Although much has been achieved in developing anti-cancer therapies, drug resistance remains one of the significant problems of cancer therapies [164,165]. Tumor resistance relates to the ability confined to cancer cells to neutralize the favorable impacts of anti-cancer substances. It may be primary or secondary—implying that it arises from within the tumor or is characteristic of the growth that has not undergone these changes after the first treatment in the second instance [166]. These include genetic mutations and epigenetic changes, which are related to the acquisition of resistance due to increased drug pump activity, alterations to drug handling, and modifications to the tumor environment [167]. The emergence of the multiple-drug resistance mechanism, wherein cancerous cells may withstand various chemically dissimilar treatments and drugs, remains a significant challenge.

Both the collection and usage of data have transformed the ways of studying and combating cancer drug resistance [168]. The rapid advancement in omics technologies, including genomics, transcriptomics, proteomics, and metabolomics, has provided enormous amounts of big data describing cancer's molecular characteristics [169]. The biomarkers related to drug resistance and possible therapeutic methods have been discovered using these datasets. For instance, next-generation sequencing (NGS) has been instrumental in the detection of resistance-associated mutations, including the EGFR in lung cancer or the BRCA genes in breast and ovarian cancer [170,171].

Data accumulation also contributes to understanding factors determining drug response and creating corresponding predictive models [172]. Machine learning techniques and artificial intelligence are currently used to process high-dimensional data to predict drug resistance mechanisms and drug discovery [173]. Moreover, large-scale datasets, including The Cancer Genome Atlas and Genomics of Drug Sensitivity in Cancer, are available, which allows researchers to study the relationship between genetic alteration and drug sensitivity [174].

When it comes to the issue of toxic exposure in the working environment, knowledge at the molecular level of cancer becomes significant. External and workplace carcinogens may lead to mutagenic genetic and epigenetic modification of workers' genomes, resulting in drug-resistant cancers [175]. VOCs have been found to have tumorigenic properties in relation to human beings and animals with different campaigns. Investigations into how individual VOCs interact with targets such as drug receptors and affect consequent cellular outcomes could assist in developing therapeutic interventions to deal with VOC-mediated occupational hazards and cancer drug resistance [176].

Therefore, combining the massive collection of information with recent technologies such as computational algorithms have high possibilities for succeeding in the absence of cancer drug resistance. This interface of science and technology permits the precision medical management of cancer health, which boosts the cross possibilities and consequences in policy, economics, and international health domains, especially in cases of occupational health dangers.

15. Future Directions on the Mechanisms and Clinical Applications of VOC–Receptor Interactions in Occupational Health

Integration of Advanced Technologies: Advanced technologies like artificial intelligence (AI), machine learning (ML), and high-throughput screening can further advance the analysis of VOC–receptor interactions and drug design. Using AI and ML concepts, one can identify the patterns in the big data and define the patterns of the interactions. At the

same time, high-throughput screening allows the screening of several compounds based on receptor activity. Such technologies have the potential to reduce the time used in drug discovery, enhancing the precision of the predictions, as well as finding other targets for the treatment of VOC-induced toxicity.

Personalized Medicine Approaches: Biomolecular phenotyping methods, such as genetic, epigenetic, and metabolic backgrounds of patients, can enhance the quality and safety of the therapy for VOC-induced toxicity by adjusting or selecting individualized treatments. Individualized treatments enable investigators to achieve the best results of a therapeutic process and simultaneously exclude the appearance of undesirable side effects. Progress in both the fields of omics and bioinformatic knowledge may help create individual approaches for handling VOC exposure and its effects on health.

Environmental and Occupational Health Policies: Policies relating to environment and occupational health must be enhanced to help minimize the emission of VOCs and safeguard people's health. It is best to concentrate on developing exposure standards, observing compliance with safety measures, and disseminating information about good practices within workplaces and other areas. Healing programs and public awareness can inform people about the dangers that exist in exposure to VOC and the necessary protective measures to employ. In this case, one way to come up with and administer policies within this area that would reduce the health risks associated with VOCs is through policy cooperation between policymakers, researchers, industry players, and other relevant tripartite players.

Global Health Initiatives: International health policies that relate to VOC and its effects on the well-being of the people can foster research, policy, and public health practice all over the globe.

Awareness raising: International collaborations and partnerships help spread knowledge, ideas, and possible practices, enhancing the establishment of an international approach and strategy for resolving VOC detoxification. Such initiatives also lobby for more rigid policies and protective measures from social hazards to ensure healthier populations in the global society.

The investigation of VOCs and their behavior with drug receptors presents novel approaches to drug design, especially with emerging topics such as toxic occupational exposure [163]. Moving forward, there is the probability that various computational modelling approaches will be on the frontline in increasing our understanding of the VOC–drug receptor relationships [164]. It is, therefore, possible to achieve exact conclusions regarding binding affinities and interaction profiles of designed systems using molecular docking, dynamic simulations as well as machine learning algorithms. They also enable the identification of VOC-associated metabolic processes and how these might influence drug effects, particularly in conditions such as cancer, where cellular environments are complex and rapidly changing [165].

Nevertheless, structure–activity relationship (SAR) studies will continue to be an essential tool for this field. Also, by comparing the structure of VOCs to their biological activities, SAR studies can point out molecular features that determine receptor binding and activation [73]. These perceptions can inform the logical engineering of drugs that would help counter the impact of toxic VOCs, which industrial workers increasingly contend with. Such strategies are especially useful in cancer research because VOCs might lead to cancer development and progression [72].

The problem of cancer drug resistance is considered a major current health challenge. Emerging trends focus on the future utilization of structural investigations of VOC–drug receptor interplays. For instance, VOCs associated with computational pan-cancer screening can uncover core biomarkers of resistance mechanisms across different cancers [166,167].

This approach helps develop specific therapies and re-engineer existing drugs to overcome resistance and become more effective. Indeed, including VOC data in calculative models can reveal new targets for intervention, thereby informing the design of suitable inhibitors or modulators highly specific to the targets.

Moreover, recent developments in artificial intelligence (AI) and quantum computing are expected to impact this field. AI models can simultaneously analyze the results of high-throughput VOC screenings and identify patterns and interactivity beyond human understanding [75]. While computational systems can model and predict complex molecular interactions, quantum computing can enhance the precision of calculations many times over to expand what scientists can investigate within molecular systems [94].

Indeed, integrating computational modelling and SAR, along with the successful use of advanced analytical approaches, can open the vistas for the objective design of drugs related to VOCs. Against such issues as drug resistance and toxicity, these novel instruments have the potential to produce sufficient remedies for occupational exposure toxicities as well as cancer that might result from such. More interdisciplinary collaboration is needed to fully exploit this potential and bring it to its utility in the clinic.

16. Conclusions

Understanding the structure of VOC–drug receptor interactions would be very beneficial in creating treatment methods for reducing VOC toxicity. It is crucial to note that solving the problems related to this sphere can be achieved by developing technology, integrating approaches from different specialties, and identifying the processes involved. Through these approaches and emphasizing individualized medicine, prevention strategies, and strict and efficient policies, much can be achieved in defending occupational health and developing more effective means of tackling the VOC threat and its repercussions.

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