Role of black turmeric bioactive compounds on respiratory disorders

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1. Abstract: Chronic Obstructive Pulmonary Disease is leading cause of death worldwide. Chronic respiratory disorders are diseases that affect the airways and other lung structures. Asthma and chronic obstructive pulmonary disease are two of the most frequent (COPD). Asthma is a chronic, non-communicable condition characterized by repeated bouts of shortness of breath and wheezing that vary in intensity and frequency from person to person. A perennial herb of the Zingiberaceae family, commonly referred to as "Black Turmeric," with a bluish-black rhizome. Because of its unparalleled medical capabilities, this species has been steadily gaining recognition among interested parties. However, Curcuma caesia Roxb. is a relatively little-known and practically unexplored medication that traditional healers utilize in ethnomedicinal techniques to cure a variety of ailments. Researchers have looked into the plant's rhizomes for its potential as an analgesic, an anti-asthmatic, a smooth muscle relaxant, and an antifungal effects, anticonvulsant, muscle-relaxing, anxiolytic, CNS-depressant, antibacterial, and ulcer-healing properties, as well as actions that reduce locomotor activity as well as a variety of other things. Blac turmeric has many compounds in it that can help in respiratory disorders. In this review paper we will discuss potential benefits of compounds that are present in black turmeric.

***Keywords*: Black turmeric, asthma, respiratory disorder, camphor, Eucalyptol**

2. Introduction of Respiratory disease and black turmeric

Chronic Obstructive Pulmonary Disease (COPD) is the third leading cause of death worldwide, causing 3.23 million deaths a year. Over 80% of these deaths occurred in low- and middle-income countries. Chronic respiratory diseases (CRDs) are conditions that affect the airways and other lung components. Chronic obstructive pulmonary disease (COPD), asthma, occupational lung disorders, and pulmonary hypertension are among the most common. Nonetheless, they have been largely ignored in the worldwide health and development agenda. Chronic respiratory disorders such as asthma and chronic obstructive lung disease kill over four million people and affect hundreds of millions more. These disorders deteriorate patients' health and well-being and have a negative influence on families and societies. Women and children are particularly vulnerable, particularly in low and middle-income nations where they are exposed to indoor air pollution from solid fuels used for cooking and heating on a regular basis. Tobacco smoking is the most prominent risk factor for chronic respiratory diseases in high-income nations. It is still increasing among women and young people in some of these countries. Other risk factors, in addition to tobacco smoke, include air pollution, occupational toxins and dust, and repeated lower respiratory illnesses throughout childhood. CRD (Chronic Respiratory Disease) are not curable; however, several forms of treatment that help widen major air passageways and relieve shortness of breath can help control symptoms and enhance people's quality of life. Chronic respiratory disorders are diseases that affect the airways and other lung structures. Asthma and chronic obstructive pulmonary disease are two of the most frequent (COPD). Asthma is a chronic, non-communicable condition characterized by repeated bouts of shortness of breath and wheezing that vary in intensity and frequency from person to person. In affected individuals, symptoms may appear multiple times during the day or week, and for some, they worsen after physical activity or at night. Asthma is the most prevalent chronic condition among children. COPD is not a single disease but an umbrella term for chronic lung diseases that produce airflow limitations in the lungs. COPD's most typical symptoms are breathlessness, or a "demand for air," increased sputum production, and chronic cough.

Traditional medicine's potential may be underestimated. Alternative and complementary medicine are widely practiced in many countries. Traditional medicine is particularly important in low and middle-income nations, where it is frequently the only available remedy. Because of patient beliefs and taboos, the inaccessibility of health care, and the high expense of drugs, treatment with traditional remedies are frequently the initial step in the management of diseases. In many locations, traditional and contemporary medicine have coexisted. Because prescription prices are often prohibitively high, the use of appropriate traditional medicine was encouraged at the Fifty-fifth World Health Assembly. There are some herbs that are helpful in CRD, for ex. Astragalus, Pippali, Licorice, Kalmegh, Vasaka, Turmeric, Peppermint, Ginger, Cardamom, Cardamom. These herbs have a significantly beneficial role in it. In all, there is the herb **Black turmeric** that helps with many diseases. In this review paper, we will discuss black turmeric and its compounds in it that contribute to its beneficiary role in treating CRD.

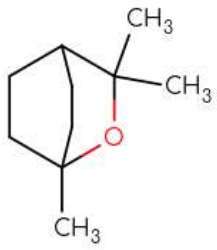
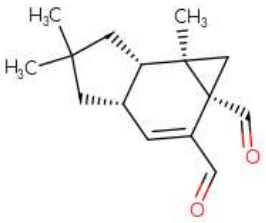
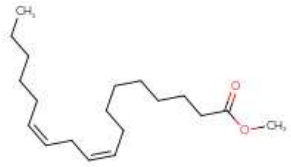
Black turmeric

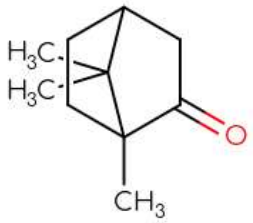
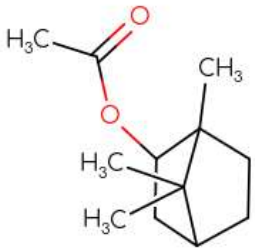
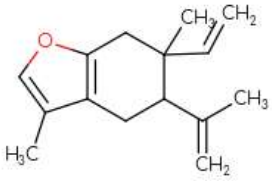
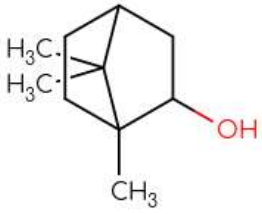
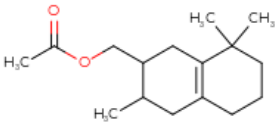
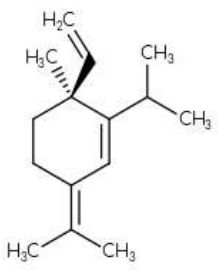
Curcuma is a well-known spice from India. It is also known as Haldi, and there are over 200 species and subspecies of it found all over the world. It is sometimes referred to as "Kali Haldi." It is a rhizomatous erect herb with big leaves. Curcuma caesia Roxb. is a member of the Zingiberaceae family and is often known as Kali Haldi. It is found in the Indian states of West Bengal, Madhya Pradesh, Orissa, Chhattisgarh, and Uttar Pradesh. It thrives in damp deciduous forest environments. It can also be found in the Papi hills of East Godavari, the Himalayan root highlands, and the North Hill forest of Sikkim. The plant's rhizomes are used to treat sprains and bruises, as well as to make cosmetics. Because of their potential medicinal characteristics, the rhizomes of Black Turmeric have significant economic value. Rhizomes are used to cure haemorrhoids, leprosy, asthma, cancer, epilepsy, fever,

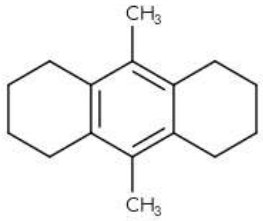
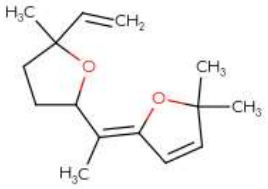
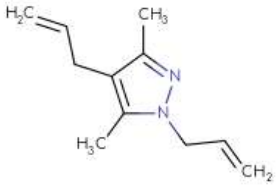
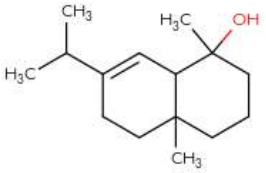
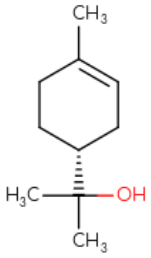
wounds, vomiting, menstrual disturbances, smooth muscle relaxant activity, anthelmintic, aphrodisiac, inflammation, gonorrheal discharges, and other conditions. Almost all Curcuma species have antioxidant activity and pharmacological effects. (Pathan et al.,2013)

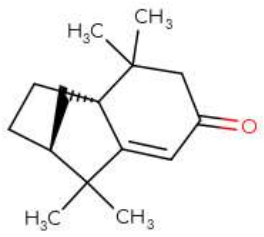
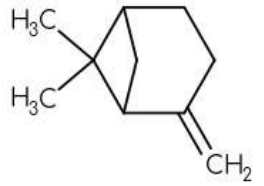
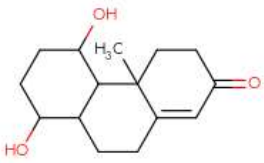
3. The natural compound present in Black turmeric

The rhizomes of C. caesia Roxb. were collected from the Pasighat district of Arunachal Pradesh, India. The essential oil was extracted from the freshly cut rhizomes of C. caesia essential oil (CCEO) by hydrodistillation for 8 h using a Clevenger-type apparatus. A pale yellow-colored oil was collected in a sterilized amber-coloured glass vial and stored at 4°C for further analysis. Constituents of CCEO were quantified and identified by **gas chromatography-mass spectrometry** (GC-MS) on an Agilent 5921A gas chromatograph hooked to an Agilent 5975 mass selective detector. GC was outfitted with HP-5MS (30 m × 250 µm × 0.25 µm). Initially, the oven temperature was held at 50°C for 1 min and ramped at 20°C/min to 200°C for 1 min. The injector temperature was maintained at 280°C. The sample of 10 µL volume was diluted to 1% with methanol and then injected by the splitless method. Helium was chosen as a carrier gas at the flow rate of 1 mL/min. Scanning of spectra was done in the range from 50 m/z to 550 m/z at 3 scans per second. The chromatogram obtained was compared with the data stored up in NIST08 (NIST, Gaithersburg, MD, USA) and W8N08 (John Wiley and Sons, Inc., USA). Following constituents were determined.

Name of Compound	CAS No.	Structure	Therapeutic values
Androsta-1,4-dien-3-one, 17-(acetyloxy)-, (17.beta.)- Santanol acetate			
Eucalyptol	470-82-6		Eucalyptol is a monoterpenoid oil present in many plants, It has anti-inflammatory and antioxidative effects. Eucalyptol controls airway mucus hypersecretion and asthma via anti-inflammatory cytokine inhibition.
Isovelleral	37841-91-1		Interaction at vanilloid receptors, interaction at other receptors and toxicity to mammalian cells, Phytotoxicity, Antibacterial activity, Antifungal activity, mutagenicity
Methyl linoleate	112-63-0		Methyl linoleate has been tested against inhibition of the in vitro proliferation of human tumor cell lines; It contain antifungal and antioxidative properties as well

(+)-2-Bornanone (Camphor)	76-22-2		The potent antifungal, anti-inflammatory and antibacterial properties promote respiratory health, heal skin disorders and ease the pain.
Bornyl Acetate	92618-89-8		Analgesic and anti-inflammatory activities antiasthmatic effect bornyl acetate could be exerting anti-abortive effect through modulation of maternal-fetal interface immunity balance
Curzerene	17910-09-7		Antiproliferative and cytotoxic effect against some cancer strains , antioxidant activity
Isoborneol	507-70-0		Isoborneol has antiviral properties and is a potent inhibitor of herpes simplex virus type,anti-oxidant properties and neuroprotective effect
Acetic acid, (1,2,3,4,5,6,7,8-octahydro-3,8,8-trimethylnapth-2-yl) methyl ester	314773-27-8		
(-)- beta- Elemene	5951-67-7		β-elemene exerts its effects by inhibiting cell proliferation, arresting the cell cycle, inducing cell apoptosis, exerting antiangiogenesis and antimetastasis effects, reversing multiple-drug resistance (MDR), and enhancing the immune system.

Anthracene, 1,2,3,4,5,6,7,8-octahydro-9,10-dimethyl	42173-25-1		
Davana ether	35470-57-6		Its properties as an anti-depressant, antiseptic, antiviral, disinfectant, emenagogue, expectorant, relaxant, and vulnerary substance are well known.
3,5-Dimethyl-1,4-diallylpyrazole	Inchl key- BYQUXKFPPIMUKC-UHFFFAOYSA-N		
(E, E)- Germacrone or 3,7-Cyclodecadien-1-one, 3,7-dimethyl-10-(1-methylethylidene)-, (E, E)-	6902-91-6		It inhibits influenza virus replication. Germacrone showed antiviral activity against the H1N1 and H3N2 influenza A viruses and the influenza B virus in a dose-dependent manner. Germacrone also showed antiproliferative effects via cell cycle arrest
Selina-6-en-4-ol	Inchl key-PBGYWCDUYHJYFV-UHFFFAOYSA-N		
Alpha.-Terpineol	7785-53-7		α-terpineol attracts a great interest as it has a wide range of biological applications as an antioxidant, anticancer, anticonvulsant, antiulcer, antihypertensive, anti-nociceptive compound. It is also used to enhance skin penetration, and also has insecticidal properties.

Isolongifolenone	26839-52-1		Isolongifolenone has been used as a bridged core to prepare a chiral ligand for the estrogen receptor that could be useful in regulating fertility, preventing, and treating breast cancer, and for menopausal hormone replacement
(-)- β- Pinene	127-91-3		It is known to possess antimicrobial, apoptotic, antimetastatic, and antibiotic properties (Cote, n.d.). α-pinene is one promising agent for the treatment of various inflammatory diseases as it has been found to suppress MAPKs and the NF-κB pathway
5,8-Dihydroxy-4a-methyl-4,4a, 4b, 5,6,7,8,8a, 9,10-decahydro-2(3H)-phenanthrenone	Inchl key-AOMIEBNQFOURPP-UHFFFAOYSA-N		

4. Compound effects on respiratory disease

4.1. 1, 8-cineole(Eucalyptol)

Pre-clinical studies on the mechanism essential oil of eucalyptus in respiratory disease

Several research have been undertaken in preclinical respiratory disease models to provide information on the potential mechanism(s) of eucalyptol in the treatment of inflammatory or infectious respiratory sickness. An investigation in lipopolysaccharide (LPS) stimulated monocytes with eucalyptol at 1.5 µg/ml demonstrated significant decreases in production of the pro-inflammatory cytokines tumour necrosis factor-alpha (TNF-α) and interleukin-1-beta (IL-1b) ranging from 65 to 92%.

Ex-vivo human monocytes treated with eucalyptol 200 mg three times daily for three days by mouth showed a 30–60% suppression of various cytokines and inflammatory factors including TNF-, IL-1b, leukotriene B4 (LTB4), and thromboxane B2. A study in human cell lines employing LPS as an inflammatory stimulant found that a 0.6 mg/L eucalyptol extract might reduce inflammation by suppressing the inflammatory gene promoter NF-κB p65 compared with a control group ($p < 0.01$). Recently, it was discovered that eucalyptol pretreatment can downregulate pattern recognition receptors involved in LPS signalling, resulting in lower phosphorylation of downstream transcription factors NF-κB and p38. The anti-inflammatory properties of eucalyptol were also shown to be reduced by deleting the gene coding for the transient receptor potential member 8 (TRPM8) channel. Eucalyptol has been demonstrated to reduce mucus production by 66% in human ex-vivo monocytes simulating rhinosinusitis by downregulating mucous production genes, MUC2 and MUC19. Aromatic chemical preparations containing eucalyptol (as well as other aromatics) were found to increase mucociliary clearance and mucociliary beat frequency. Eucalyptol has been demonstrated to have a relaxant or bronchodilatory effect in guinea pig smooth muscle from airways. There have also been studies that show eucalyptol has antinociceptive effects and reduces neuropathic pain signals. The data suggest that eucalyptol possesses anti-inflammatory, expectorant, bronchodilator, and analgesic actions; all of which may be beneficial in respiratory disorders such as asthma, chronic obstructive pulmonary disease (COPD), bronchitis, or other conditions characterised by cough.

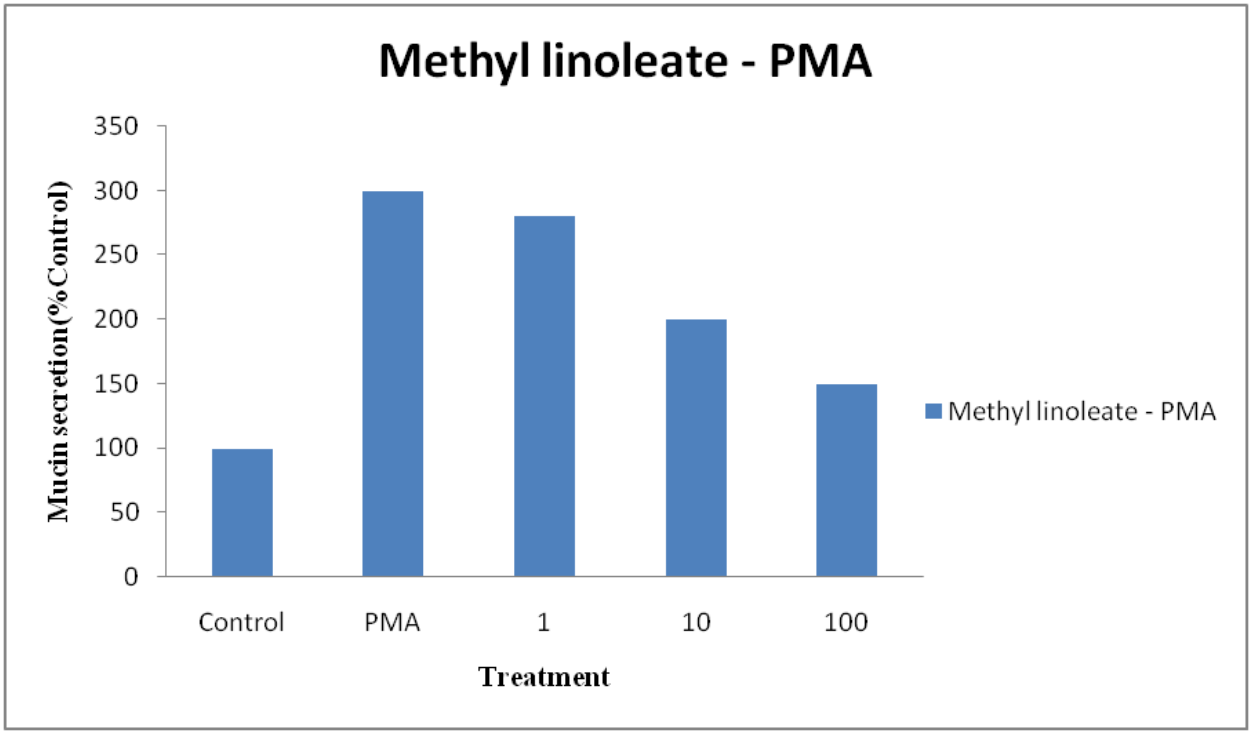
Pharmacokinetics and drug interaction potential

Eucalyptol is fast absorbed and can be seen in the blood after 5 minutes of inhalation, while it reaches its highest plasma concentration around 18 minutes after inhalation. Following oral administration in gastro resistant capsules, eucalyptol is absorbed through the small intestine and then hepatic conversion by human cytochrome P450 enzymes (CYP3A4/5) into its main metabolites of 2--hydroxy- and 3--hydroxycineole, which are eliminated in urine. It is also expelled through expired air, implying that eucalyptol might enter the lungs, peripheral airways, and sinuses following oral consumption. Previous research of the metabolism and pharmacokinetics of eucalyptol in rats and humans discovered that aerosolized eucalyptol was capable of affecting plasma concentrations of other medications. For four days, rats were aerosolized with eucalyptol or a placebo for 5-10 minutes. When compared to controls, brain concentrations of aminopyrine, amphetamine, zoxazolamine, and pentobarbital were considerably lower

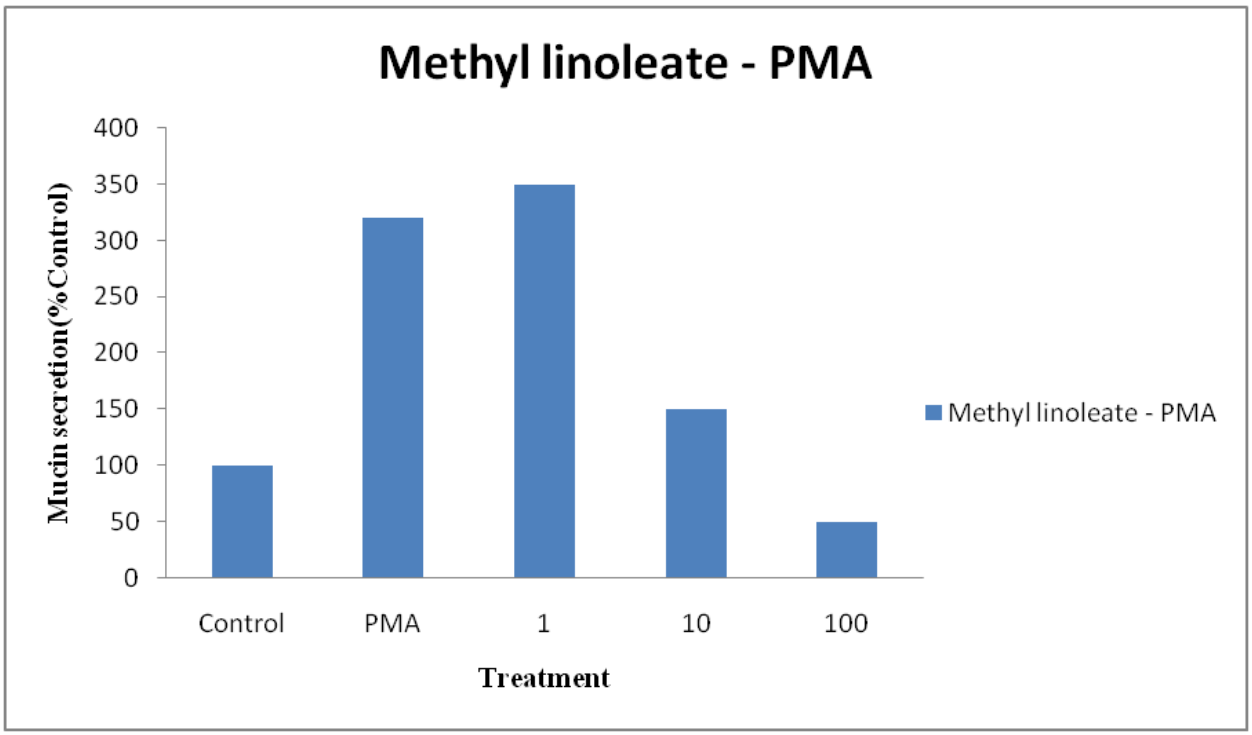
2-6 hours after drug delivery. Four of five healthy human volunteers who received aerosolized eucalyptol for 10 minutes every day for ten days saw an increase in aminopyrine plasma clearance. All medicines were supplied 24 hours after the last aerosolization, and the authors conclude that eucalyptol is likely a hepatic cytochrome P450 (CYP) inducer even when administered by inhalation. Surprisingly, subsequent in vitro research evaluating CYP inhibitory efficacy in baculovirus-infected insect cells discovered that eucalyptol inhibited CYP 1A2, 2C8, 2C9, 2C19, and 3A4, particularly at 100 and 500 µg/ml doses. Potential pharmacokinetic medication interactions with eucalyptol via CYP induction or inhibition need further investigation. (Galan, Derick M., et al. 2020)

4.2 Methyl linoleate

The hallmark risk factor of asthma is airway mucin overproduction, which is associated with decreased lung function. Because of its high viscosity, an abnormal mucin expression causes airway blockage. MUC5AC is the primary mucin of airway epithelia among the mucins found. Mucin-induced asthma and chronic obstructive pulmonary disease (COPD) are major concerns nowadays. PMA(phorbol 12-myristate 13-acetate) activates a type of PKC(protein kinase C) isoforms. This activates matrix metalloproteinases, which cleave pro-epidermal growth factor receptor (pro-EGFR) ligands from the cell surface to become mature EGFR ligands. These ligands bind to the EGFR, provoking the phosphorylation of its intracellular tyrosine kinase. This leads to activation of MEK (**Mitogen-activated protein kinase**) leading to ERK(extracellular signal-regulated kinase) activation. Following is the activation of the transcription factor, Sp1, and binding of the factor to specific sites with the *MUC5AC* gene promoter. Eventually, the promoter is activated and produced the gene transcription and translation to MUC5AC mucin protein methyl linoleate suppressed PMA-induced MUC5AC mucin production from NCI-H292 cells. Methyl linoleate showed consistent inhibitory activities on secretion, production and gene expression of airway MUC5AC mucin, by directly acting on airway epithelial cells. The underlying mechanism of action of methyl linoleate on MUC5AC secretion, production and gene expression is not clear at present, (Yoon YP, Ryu J, Park SH, et al (2014))



Effect of methyl linoleate (C) on phorbol 12-myristate 13-acetate (PMA)-induced MUC5AC mucin secretion from NCI-H292 cells. NCI-H292 cells were pretreated with varying concentrations of, or methyl linoleate for 30 minutes and then stimulated with PMA (10 ng/mL) for 24 hours. Spent media were collected for measuring MUC5AC mucin secretion by enzyme-linked immunosorbent assay. experiments were performed and the representative data are shown.



Effect of methyl linoleate (C) on phorbol 12-myristate 13-acetate (PMA)-induced MUC5AC mucin production from NCI-H292 cells. NCI-H292 cells were pretreated with varying concentrations of , or methyl linoleate for 30 minutes and then stimulated with PMA (10 ng/mL) for 24 hours. Cell lysates were collected for measuring MUC5AC mucin production by enzyme-linked immunosorbent assay Experiments were performed and the representative data are shown. (Yoon YP, Ryu J, Park SH, et al (2014))

4.3 Bornyl Acetate

Acute lung injury and acute respiratory distress syndrome (ALI/ARDS) are major causes of mortality in intensive care units, and are characterized by hypoxemia, pulmonary infiltration, absence of an elevated pulmonary capillary wedge pressure, pulmonary neutrophil sequestration, intravascular coagulation, disruption of pulmonary capillary integrity leading to edema, and increased shunt fraction. The most severe form of ALI is ARDS, which is a major cause for admission to critical care units

Bornyl acetate exerts anti-inflammatory effects on LPS-stimulated RAW 264.7 cells and an LPS-induced murine model of ALI. The study primarily focused on anti-inflammatory effects of bornyl acetate on LPS-stimulated RAW 264.7 cells. LPS stimulates macrophages to release proinflammatory and antiinflammatory factors, followed by a series of physiological and pathologic reactions. Excessive production of proinflammatory cytokines not only enhances the immune responses by fighting invading pathogens but also has deleterious effects, such as perturbing regular hemodynamic and metabolic balances. Bornyl acetate obviously alleviated LPS-stimulated cytokine secretion. ALI/ARDS is defined by physiological and radiographic criteria, and comprises a major cause of high morbidity and mortality in critical care medicine. LPS-induced ALI is characterized by the infiltration of neutrophils and macrophages in alveoli, the release of chemokines, and proinflammatory cytokines from activated macrophages and neutrophils, such as IL-1b and TNF-a. In this study, we also found that bornyl acetate significantly lowered the production of the LPS-induced proinflammatory cytokines, such as TNF-a, IL-1b, and IL-6. Accumulating evidence has indicated a consistent association between neutrophils and ALI in humans and animal models, and the propensity of neutrophils and their products to cause tissue injury in experimental systems, leading to the conclusion that neutrophils have an important causative role in ALI . Therefore, neutrophils are considered to be central to the pathogenesis of most forms of ALI. In this study, we first investigated the differential cell count in BALF (Bronchoalveolar lavage fluid) of ALI mice and found that the total cohort of inflammatory cells in bornyl acetate pretreated groups, including macrophages and neutrophils, was markedly reduced compared with the LPS group. Then we evaluated the W/D ratio of the lung and the results showed that bornyl acetate significantly decreased the ratio, which indicates that bornyl acetate could inhibit the leakage of serous fluid into lung tissue. As a proteinase is highly expressed in neutrophils, MPO (Myeloperoxidase enzyme) is the major indicator of neutrophil infiltration. LPS caused a significant upregulation of MPO activity in the lung tissues, whereas bornyl acetate successfully reduced MPO activity. Additionally, the histopathologic results also indicated that bornyl acetate pretreatment markedly attenuated neutrophil infiltration into the lungs. Both the reduced MPO activity and histopathologic alterations paralleled the results of cell counts in the BALF. As upstream signal molecules of proinflammatory mediators, MAPKs, and NF-kB are considered to play vital roles in regulating these productions of inflammatory mediators in response to a broad range of stimuli, including heat shock, microbial infection, and ischemia-reperfusion. The MAPK family consists of three different subgroups of molecules: ERK1/2, JNK, and p38 MAPK. The activation of the p38 pathway plays an essential role in the production of proinflammatory cytokines, such as IL-1b, TNF-a, and IL-6. On the other hand, NF-kB is a key transcription factor in response to host defense against infection. Under the unstimulated conditions, NF-kB is present in the cytosol and is bound to inhibitory protein IkB. After LPS challenge, NF-kB is translocated into the nucleus to drive

the expression of a variety of inflammatory genes, which are involved in the pathogenesis of ALI. NF-kB activation is an indispensable event in a variety of lung diseases, including ALI/ARDS, asthma, and respiratory viral infections, systemic inflammatory response syndrome, and occupational and environmental lung diseases. Greater or more persistent activation of MAPKs and nuclear accumulation of NF-kB are associated with higher mortality and more persistent organ dysfunction, including pulmonary injury. Therefore, blockade of MAPKs and NF-kB activation, which mediates the expression of proinflammatory mediators, appears to be a logical therapeutic target for controlling hyperinflammatory responses, including ALI. To confirm whether bornyl acetate modulates the activation of these upstream signal molecules, the Western blotting method was used to investigate the expression of phosphorylated ERK1/2, JNK, p38, and IkB. The activation of these signalling molecules was suppressed by bornyl acetate in a dose-dependent manner, suggesting that the protective effects of bornyl acetate on LPS-induced ALI may be linked to the inhibition of the activation of MAPKs and NF-kB signalling pathway. (Chen, Na, et al. 2014)

4.4 α-Terpineol

Bronchial asthma is a common, chronic respiratory disease affecting 1-18% of the population in different countries and is characterized by bronchoconstriction, airway hyperresponsiveness, mucus secretion, and chronic inflammation. Of these symptoms, the decreased lung function observed in bronchial asthma is due to the contraction of airway smooth muscle (ASM) and chronic inflammation. It is not only a serious influence on people's normal life, even life-threatening to patients. However, there's no radical cure means for asthma treatment so far. The treatment and prevention of asthma is only by effective drug to improve symptoms α-terpineol (α-T) has multiple pharmacological functions, including relaxation of tracheal smooth muscle, as well as the expectorant, antitussive, anti-inflammatory, and anti-allergic effects. Although α-terpineol didn't show the adverse effects of β2-agonists byaerosol inhalation for the treatment of asthma. A series of novel α-terpineol derivatives were designed and synthesized through structural derivatization of the tertiary hydroxyl moiety or reduction of the double bond. Of the resulting compounds, eight compounds enhanced relaxation of airway smooth muscle (ASM) compared to the α-terpineol precursor, and four compounds （4a, 4d, 4e, and 4i） were superior or comparable to aminophylline at a concentration of 0.75mmol/L. Assays for 3'-5'-Cyclic adenosine monophpsphate (cAMP) activation revealed that some representative α-terpineol derivatives in this series were capable of upregulating the level of cAMP in ASM cells. Further in vivo investigation using the asthmatic rat model, illustrated that treatment with the compounds 4a and 4e resulted in significantly lowered lung resistance (RL) and enhanced dynamic lung compliance (Cldyn), two important parameters for lung fuction. Moreover, treatment with 4e downregulated the levels of both IL-4 and IL-17. Due to its several favorable physiological functions, including ASM relaxation activity, cAMP activation capability, and in vivo anti-asthmatic efficacy, 4e is a promising remedy for bronchial asthma, meriting extensive

ASM relaxation assay

The hyperresponsiveness of airway, namely the excessive contraction of airway, is a risk factor for the development of asthma, and is also an important endpoint evaluation index for the efficacy of asthma. Therefore, medication by alleviating the excessive contraction of the bronchial smooth muscle (i.e., the high reactivity of airway) that is one of the targets to treat asthma. The relaxation efficacy of all of the target compounds were evaluated via ASM relaxation assay using aminophylline, a anti-asthmatic agent in clinic, α-terpineol derivatives exhibited relaxation activity in a dose-dependent manner. Among them, half of the tested compounds showed relaxation effects with similar or more potency to that of α-terpineol.

Biological assay

Guinea pig tracheal smooth muscle rings were incubated in organ baths filled with Krebs-Henseleit solution and supplied with a plentiful mixture of 95% O2 and 5% CO2 at 36.5±0.5°C. Alterations in the tension of the isolated guinea-pig tracheal strips were input into the signal collection and processing system through a tension transducer Before each experiment, a resting tension of 1.0 g was applied to each strip, followed by a 60-minute equilibration. Isometric tension measurements were obtained through observation of the alteration in the tension of isolated guinea pig tracheal rings contraction in response to acetylcholine (Ach), and calculated as the percentage change of smooth muscle tension for the tested compounds

Anti-asthmatic assay

α-Terpineol and dexamethasone acetate were used as positive control. The smooth wheezing effect of compounds was assessed via two lung function parameters, airway resistance (RL) and the dynamic compliance of the airway (Cldyn). While the former reflects the resistance of the respiratory tract to airflow during inspiration and expiration, the latter is involved with the lung'sability to stretch and expand during actual movement of air. In addition, the assay also evaluated the levels of IL-4 and IL-17, which serve as asthma proinflammatory cytokines and play vital roles in recruiting eosinophils and neutrophils, In treatment with α-terpineol derivatives led to significantly lowered RL and enhanced Cldyn. (Zhu, Wanping, et al., 2018)

Biological assay

Sixty male Sprague-Dawley rats (200±20 g, purchased from the Animal Center of Zhejiang Academy of Traditional Chinese Medicine) were randomly divided into 6 groups (n=10 each): control group, model group, α-terpineol group, Dexamethasone Acetate group, compound 4a group, and 4e group. Rats were maintained in an animal facility for 5 days prior to experimentation. All animals were provided water and standard chow ad libitum. All procedures in the experiment were performed in accordance with the Guide for Care and Use of Laboratory Animals, published by the U.S. National Institutes of Health . Animals were sensitized with an intraperitoneal injection of 100 mg OVA and 100 mg aluminum hydroxide in 1 mL normal saline (NS) on days 1 and 8, and then challenged from days 15 to 21 with OVA (1%, w/v, in NS) . Meanwhile, the treatment was done on days 15 to

21, too. The 4a and 4e groups received compounds at a dosage of 1.6 g/kg through oral administration. The α-terpinene group was treated with an oral dosage of 1.0 g/kg. The positive group was treated with an oral dosage of 0.5 mg/kg of dexamethasone acetate tablets, while the control group and the model group received an equal volume of saline solution.The challenge of all groups, with the exception of the normal group, was executed with OVA (1%, w/v, in NS) using a medical ultrasonic nebulizer (BSE2A, Beijing daya technology co., LTD, China) for 30min after the delivery as described. Animals were narcotized immediately after the final challenge with 10% ethyl carbamate (1300 mg/kg) for lung function tests using a biological signal collecting and handling system (U/4C501H, Nanjing yi technology co., LTD, China). The abdominal venous blood was collected and later subjected to centrifugation (3000 rpm, 10 min) in order to obtain serum for assaying of IL-4 and IL-17.

cAMP activation assay

cAMP is the second messenger in the cell, which play key roles in bronchial smooth muscle relaxation, stability of mast cell, and the bronchial cilia movement. Based on the results of the ASM relaxation assay, the representative α-terpineol derivatives 4a, 4b, 4d, 4e, 4g, 4h and 4j, were further assessed for their capability of upregulating cAMP in ASM cells. All of these compounds increased the release of cAMP in ASM cells, at levels significantly higher than that of the model group ($p<0.05$). Contrastingly, neither α-terpineol nor aminophylline treatment led to a remarkable release of cAMP. Based on the above experimental results, it is noteworthy that the ASM relaxation effect of tested compounds is possible by promoting the release of cAMP (Zhu, Wanping, et al., 2018)

Biological assay

Rat airway smooth muscle cells (ASMCs) cultured between passages four and six were plated at a density of 5×104 /mL in 24-well plates and incubated for 48 hours . With the exception of the normal group, cells were then stimulated for 4 hours with the contractile agonist Ach (0.33 mmol/L) followed by incubation with various compounds for 18 hours, with the exception of the control and model groups. Then, the cultured cells were passaged following trypsinization (0.25%, 2 min). At last, cells were collected and crushed with an utrasonic cell disruptor. Supernatants were later collected and used for future cAMP analysis by ELISA.

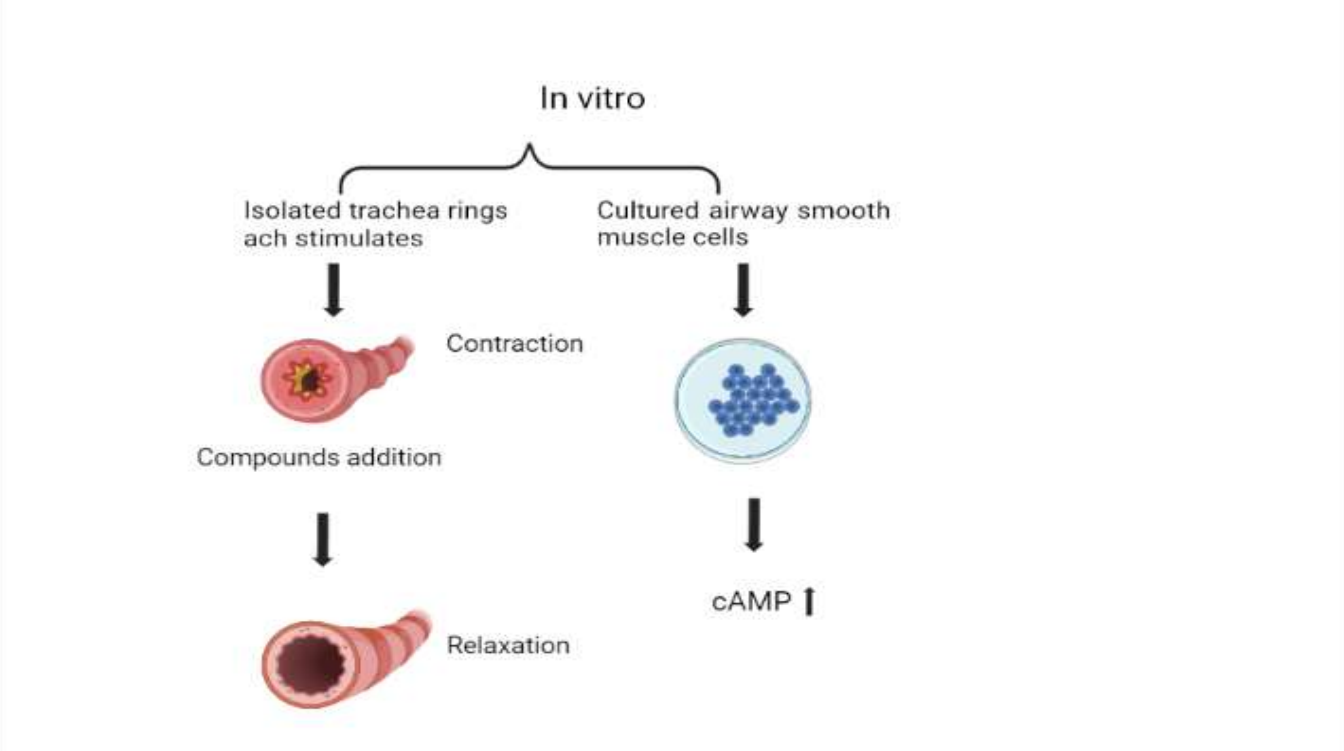


Fig - ASM relaxation effect

4.5 Isovelleral

Isovelleral is a terpenoid Similar to other unsaturated dialdehydes, this compound evokes a pungent sensation on the human tongue. Like capsaicin, isovelleral excites and then desensitizes the chemical pain pathway in the rat eye and shows cross-desensitization with capsaicin (Szallasi et al., 1996). Isovelleral induces Ca2+ uptake by rat DRG neurons in culture, an effect which is fully inhibited by the competitive TRPV1 receptor antagonist capsazepine and induces an increase in the intracellular Ca2+ concentration in human neuroblastoma SH-SY5Y cells Furthermore, isovelleral inhibits specific [3 H]-RTX binding sites in rat TG or spinal cord and in rTRPV1-HEK293 cells, In contrast, isovelleral was not active at recombinant rTRPV1-HEK293 nor at native TRPV1 in DRG neurons. Interestingly, isovelleral acts as a competitive antagonist of capsaicin responses in both rTRPV1-HEK293 cells and DRG neurons. Collectively, these findings comprise a strong argument that some effects induced by isovelleral are, at least in part, associated with its ability to interact with TRPV1. Furthermore, isovelleral seems to exhibit both agonist and antagonist properties at TRPV1 channels. However, as expected from their reactive nature, dialdehyde sesquiterpenes and other terpenoids possess additional sites of action that could be associated with the complex behavior observed, for instance, with isovelleral .(Calixto, João B. et al., 2005)

TRPV1 positive cells are found on epithelial cells, vascular endothelial cells, submucosal glands and nerves in the human nasal mucosa . In the guinea pig respiratory system, TRPV1 is found in fine axons within the epithelium of the trachea, but these TRPV1-expressing axons constitute only a fraction of the total axonal innervation of the epithelium. A population of the TRPV1 immunoreactive axons in the tracheal epithelium are devoid of substance P. TRPV1 immunoreactive axons are also found in, and around, subepithelial regions of the airways, including smooth muscle and blood vessels and within the lower airways, in the vicinity of bronchi and bronchioles, and in, and around, the alveolar tissue Almost all TRPV1 axons in the lung also express CGRP. Virtually all TRPV1 axons in the vicinity of bronchioles, alveoli, and intrapulmonary blood vessels, also express both substance P and CGRP. Chronic treatment of guinea pigs with capsaicin ablates bronchoconstrictor responses to capsaicin and is associated with a complete loss of TRPV1 immunoreactivity within the lung TRPV1 controls acid-induced, and heat-induced, CGRP release and sensitisation by bradykinin in the isolated mouse trachea . After chronic airway inflammation in rat, there is altered expression of TRPV1 and sensitivity to capsaicin in pulmonary myelinated afferents TRPV1 is found in human laryngeal epithelial cells TRPA1 is also often important in airway chemosensation and inflammation . Particulate matter-induced inflammation in both epithelial and neuronal cells may be contributed to by activation of TRPV1, ASIC1a, and ASIC3 receptors Exposure to airborne particulate-matter, comprising residual oil fly ash and volcanic ash, induces cell death in normal human airway epithelial cells and in mouse sensory neurons. Cell death is occasioned by sustained calcium influx through TRPV1 The capsaicinoids found in "pepper sprays" used for selfdefence, when inhaled by rats, via the nose, produce acute inflammation, moderate epithelial cell dysplasia and necrosis in the upper and lower respiratory tract. The most severe lesions produced are found in the terminal bronchioles and alveoli where marked inflammation, multi-focal macrophage proliferation, bronchiolar and alveolar epithelial cell injury, and middle to marked vascular congestion with septal and alveolar haemorrhage, occur. These effects appear to be initiated by activation of TRPV1 . IL-6 (a Th2 cytokine), released from airway epithelium, may play a role in the mechanisms of the pathogenesis of upper respiratory tract inflammatory diseases. Capsaicin induces production of IL-6 in human nasal and tracheal epithelial cells via activation of TRPV1. Thus, topical challenge of capsaicin to the airways may lead to inflammation caused directly by IL-6 from epithelial cells as well as neurogenic inflammation Perennial rhinitis is a common disorder causing significant morbidity and can be occasioned by factors such as mechanical obstruction, allergy, or less common factors, such as xylometazoline abuse or cystic fibrosis. Intranasal capsaicin spray provides a significant and long-term reduction of symptoms in non-allergic non-infectious perennial rhinitis patients . However, the mechanism of action of capsaicin in this context remains unknown. Cough is a major sign found in respiratory diseases. Inhalation of capsaicin induces cough in normal subjects. Increased expression of TRPV1 is found in the airway epithelial nerves of patients with chronic cough TRPV1 antagonists inhibit cough elicited by aerosol exposure of ovalbumin in sensitised guinea pigs, suggesting that TRPV1 may play an important role in inflammatory cough, specifically cough associated with pulmonary inflammation, such as that found in some asthmatic patients. Anandamide is a ligand of both cannabinoid and TRPV1 receptors. Anandamide, when given by aerosol, induces cough in conscious guinea pigs in a concentration-dependent manner. The anandamide-induced cough is significantly inhibited by pretreatment with capsazepine, a TRPV1 antagonist, while pretreatment with cannabinoid antagonists elicits no effect, suggesting that anandamide-induced cough is mediated through the activation of TRPV1 ion channels Sub-acute sulphur dioxide exposure in guinea pigs produces a pronounced neutrophilic inflammation; and an increase in the number of coughs evoked by the TRPV1 agonist, capsaicin, is associated with this pulmonary inflammation. Sulphur dioxide exposure also enhances TRPV1 activity on vagal sensory neurons, and an increase in airway sensory TRPV1 function may account for this inflammation-induced cough hyperresponsiveness NGF can enhance both cough and airway obstruction via a mechanism that involves the activation of the TrkA receptor and TRPV1 but not the p38 MAPKdependent pathway. Activation of the intracellular sub-population of TRPV1 ion channels by membrane-permeable TRPV1 agonists causes endoplasmic reticulum stress and cell death in human bronchial epithelial and alveolar cells. These findings may be of significance in the context of inflammatory lung diseases where elevated concentrations of endogenous TRPV1 agonists may well be produced in sufficient quantities to cause TRPV1 activation and the death of cells within the lung In an important study, Johansen and colleagues (2006) demonstrated that prolonged treatment of human lung epithelial cells with TRPV1 antagonists induces an increase in the plasma membrane population of TRPV1 ion channels (probably by translocation of TRPV1 ion channels from the endoplasmic reticulum to the plasma membrane) and thereby significantly increases typical responses to receptor agonists. This elevation of the cell membrane population of TRPV1 ion channels exacerbates TRPV1-mediated toxicities. Their findings demonstrate the potential negative effects that may be encountered with the therapeutic use of TRPV1 antagonists to treat various diseases, including chronic pain, bladder dysfunction, or lung inflammatory diseases (PM White, J., Urban, L., & Nagy, I. et al., 2011)

4.6 Camphor

Cold, cough, allergy, bronchodilator, and antiasthmatic drug products for over-the-counter human use: Antitussive active ingredients. The active ingredients of the product consist of any of the following when used within the dosage limits and in the dosage forms established for each ingredient Camphor is a naturally occurring compound that is used as a major active ingredient of balms and liniments supplied as topical analgesics Capsaicin and menthol, two other topically applied agents widely used for similar purposes, are known to excite and desensitize sensory nerves by acting on two members of transient receptor potential (TRP) channel superfamily: heat-sensitive TRP vanilloid subtype 1 (TRPV1) and cold-sensitive TRP channel M8, respectively. Camphor has recently been shown to activate TRPV3, and here /investigators/ show that camphor also activates heterologously expressed TRPV1, requiring higher concentrations than capsaicin. Activation was enhanced by phospholipase C-coupled receptor stimulation mimicking inflamed conditions. Similar camphor-activated TRPV1-like currents were observed in isolated rat DRG neurons and were strongly potentiated after activation of protein kinase C with phorbol-12-myristate-13-acetate. Camphor activation of rat TRPV1 was mediated by distinct channel regions from capsaicin, as indicated by camphor activation in the presence of the competitive inhibitor capsazepine and in a capsaicin-insensitive point mutant. Camphor did not activate the capsaicin-insensitive

chicken TRPV1. TRPV1 desensitization is believed to contribute to the analgesic actions of capsaicin. It found that, although camphor activates TRPV1 less effectively, camphor application desensitized TRPV1 more rapidly and completely than capsaicin. Conversely, TRPV3 current sensitized after repeated camphor applications, which is inconsistent with the analgesic role of camphor. /Investigators/ also found that camphor inhibited several other related TRP channels, including ankyrin-repeat TRP 1 (TRPA1). The camphor-induced desensitization of TRPV1 and block of TRPA1 may underlie the analgesic effects of camphor. (Xu H, J Neurosci et al., (2005).

5. Herbal products in the market for respiratory problems

Sr. No.	Brand Name	Use
1	Corezcol	Expectorant
2	Hoopinil	Cough
3	Asthimna	Asthma
4	Expectum	Expectorant
5	TrueBasics lung detox	Lung cleansing
6	Breathe free	Congestion relief
7	Respir-All	Lung infection
8	Sualin	Cough,
9	Suduri	Bronchitis
10	Kapiva lung care juice	Overall lung health
11	Lungs pure	Bronchitis
12	Infuza	Asthma
13	Joshina	Bronchitis
14	Bronchial soothe	Clear Bronchial Passages
15	Ayushwaas	strengthen lung tissues

6. Future trends

Black turmeric contains a plethora of health advantages. Farmers have started planting black turmeric more than ever in recent years as market demand has soared. It has been employed by several companies for its pharmacological characteristics due to its numerous health benefits in medicine. The rhizomes of Black Turmeric have substantial economic importance due to their potential therapeutic properties. Rhizomes are used to treat illnesses such as haemorrhoids, leprosy, asthma, cancer, epilepsy, fever, wounds, vomiting, menstrual irregularities, smooth muscle relaxant activity, anthelmintic, aphrodisiac, inflammation, gonorrheal discharges, and others. There are numerous natural treatments for CRD on the market that are really beneficial. Black turmeric has numerous chemicals that are beneficial for CRD as well as asthma, lung diseases, and pulmonary hypertension. Because there is a strong potential that black turmeric can help cure CRD. There is currently relatively little research on black turmeric, and it is rarely available in the market for consumption. As a result, it opens up a wide range of opportunities and trends for black turmeric properties. When it comes to future research, the potential of black turmeric is enormous.

7. Conclusion

The current research focuses on the plant Curcuma caesia Roxb. This study indicated that herbal products can be as effective as modern treatment and are also regarded to be safer than synthetic products. The plant's rhizomes contain sufficient bioactive characteristics. The phytoconstituents have also been discovered. The pharmacological research included in this review support C. caesia's therapeutic value. This study supports the use of Curcuma caesia as a medicinal herb to treat chronic respiratory illnesses.

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