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Review Article

Xanthine scaffold: scope and potential in drug development

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Abstract

Medicinal plants have been the basis for discovery of various important marketed drugs. Xanthine is one such lead molecule. Xanthines in various forms (caffeine, theophylline, theobromine, etc) are abode in tea, coffee, cocoa, chocolate etc. giving them popular recognition. These compounds are best known for their diverse pharmaceutical applications as cyclic nucleotide phosphodiesterase inhibition, antagonization of adenosine receptor, anti-inflammatory, anti-microbial, anti-oxidant and anti-tumor activities. These properties incentivize to use xanthine as scaffold to develop new derivatives. Chemical synthesis contributes greater diversity in xanthine based derivatisation. With highlighting the existing challenges in chemical synthesis, the present review focuses the probable solution to fill existing lacuna. The review summarizes the available knowledge of xanthine based drugs development along with exploring new xanthine led chemical synthesis path for bringing diversification in xanthine based research. The main objective of this review is to explore the immense potential of xanthine as scaffold in drug development.

Keywords: Pharmaceutical chemistry, Natural product chemistry

1. Introduction

Since ancient time natural products from plants, animals, microbes and minerals have been the repertoire for drug development. Drugs may be either directly extracted from natural sources or synthetically modified using a lead compound of natural origin. Alkaloids are one such class of compounds from natural origin [1]. Early 19th century was the beginning of isolation and characterization of many important plant alkaloids such as xanthine (1817), atropine (1819), quinine (1820), caffeine (1820) etc [1]. These alkaloids are known for their diverse roles including self preserving action, inhibitor for various enzymes of cell signaling, autoinducer, allelochemicals, sidophore, anti depressants, antibacterial activity, metabolic activities, quenching activities, etc [2, 3]. Among these alkaloids, xanthine and its natural derivatives occupy prominent place in traditional medicine. Natural xanthine derivatives such as caffeine, theophylline and theobromine are purine based nitrogenous compounds which possess certain medicinal properties that are being exploited in broader ways. These derivatives are usually known as methyl xanthine derivative commonly produced by both plants and animals [4, 5]. Synthesis of these derivatives naturally in plant is the response of defense against pathogen and predators [6]. Xanthine derivatives are widely known for their non-specific inhibition properties toward phosphodiesterase enzymes [7, 8, 9]. In recent years, the scale of clinical applications on these derivatives has been augmented. This has helped in exploring the significance of these derivatives in various therapeutics applications such as adenosine receptor antagonists, inducers of histone deacetylase activity, antitumor drugs, anti asthmatic drug, psycho-stimulant drug etc [10, 11, 12, 13, 14]. The wider pharmaceutical applications of natural xanthine derivatives has prompted medicinal chemist or pharmaceutical companies to go for certain changes over lead molecule to develop more specific compounds using synthesis methodologies [15, 16, 17, 18, 19]. In drug development process, one of the major challenges is deciding the lead molecule which would act as a scaffold to provide avenue for achieving molecular diversity. Xanthine with versatile and structurally rigid scaffold provides highest possibility for molecular diversity in constructing xanthine derivatives for combinatorial chemistry [15, 20, 21, 22, 23].

Despite wider pharmaceutical applications and belongingness to purine family, xanthine based research has not taken up full pace resulting in very few synthesized xanthine based molecules. The most prominent reason for this is unfavorable synthesis methodologies such as ring closure synthetic mechanism and classical condensation route for generation of new derivatives [12, 21, 24, 25, 26, 27, 28]. These methods do not support large scale diversity in xanthine based drug development resulting in urgent need to develop viable synthesis methods so that new xanthine based drug candidates can be introduced. Till date, there has been diminutive effort for compilation of related research works in the form of review [29]. This review

emphasizes details of xanthine and its existing derivatives in terms of structure, mechanism of action, therapeutic disease target, pharmacokinetics and biological effects of substitution, biological implications of different substitution sites and existing synthesis methods. It further explores the future perspectives of xanthine based research by coming up with innovative approach for novel synthetic method for synthesis of xanthine derivatives carried out by our research group ([30]; Singh et al., article not published). Interestingly, we explored the potential of 'xanthine' both as 'scaffold'' and as 'reaction initiator' for synthesis of biologically active xanthine derivatives.

2. Main text

2.1. Xanthine and its molecular structure

Xanthines (1H-purine-2,6(3H,7H)-diones) are purine based natural heterocyclic alkaloids. They were first discovered in 1817 by German chemist Emil Fisher and later the name 'xanthine' was coined in 1899 [13]. Under the umbrella of purine family, xanthines are considered as point of convergence because both adenine and guanine converge during metabolism at this common intermediate [6, 31]. In fact, xanthine and its derivatives act as intermediate molecules in generation of GMP, GDP and GTP via the salvage pathway inside the cells [32]. In addition, xanthine plays imperative role in catabolism of nucleotides and nucleic acids as xanthine acts as precursor of uric acid. Therefore, xanthine contains similar skeleton as that of purines which forms the building blocks of unit of life i.e. ribonucleotides (RNA) and deoxyribonucleotides (DNA). The structural resemblance with two of the important purine derivatives Adenine and Guanine; makes xanthine a good therapeutic molecule. Fig. 1 depicts the chemical structure of xanthine. The structure of xanthine consists of two
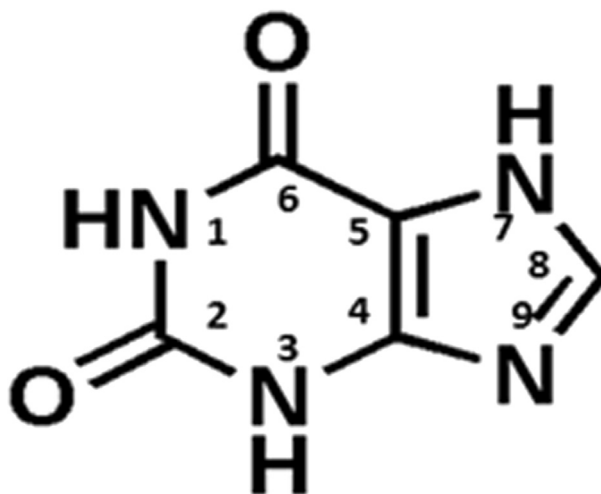

Fig. 1. Structure of xanthine.

fused rings-one ring is six membered and another is five membered. Theoretically, two types of tautomerism are displayed in xanthine molecule. First is annular i.e. migration of proton of imidazole ring between N^7 and N^9 positions. Second is lactim-lactam i.e. migration of proton between N^1 and N^3 and oxygen of carbonyl group at C^2 position [29]. Despite of annular tautomerism in xanthine, 7H form predominates over 9H form [29]. Xanthine provides maximum possibility of substitutions. Five types of mono substitutions (1-, 3-, 7-, 8- and 9-), eight di-substitutions (1,3-, 1,7-, 1,8-, 1,9-, 3,7-, 3,8-, 3,9- and 7,8-), three types of tri- substitutions (1,3,7-, 1,3,8-, 1,3,9-) [12, 21, 24, 26, 28, 29, 33, 34, 35]. Most of these substitutions are readily obtainable, but substitution at N^9 position becomes difficult because low nucleophilicity of N^9 position, electrophiles can only attack under special circumstances reference [29]. Thus, the broad understanding over reactivity pattern of the different −NH groups of xanthine have paramount importance to utilize the full potential of xanthine ring in development of xanthine based compounds.

2.2. Availability of xanthines

Numerous types of bioactive xanthine derivatives have been reported so far. These derivatives have been made available by various means including natural sources (e.g. plants, microbes, algae, animals etc), biotranformation process (via bacteria, fungi and enzyme), transmethylation process (in plants) and chemical synthesis [32]. The following section discusses about some naturally derived xanthine molecules and their sources.

2.2.1. Natural xanthine derivatives: an overview

The natural source of xanthine and its derivatives are plants as tea, coffee, cocoa seeds, etc. The presence of natural xanthine derivatives in plant is good for human health but their precise biological role in plants still needs exploration [36]. However, there are two key established hypotheses. One is their presence in young leaves and fruits act as chemical defense system for protecting plants from predators [6, 36]. Second hypothesis is allelopathic or autotoxic theory according to which the release of natural xanthine derivatives from the seed coat prevents germination of other seeds [36]. Thus, along with bearing pharmaceutical importance for others, these
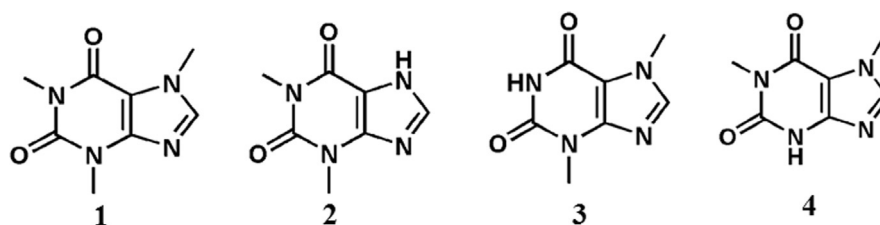

Fig. 2. Chemical structure of natural xanthine derivatives.

derivatives act as defense system for their origin too [37, 38]. Fig. 2 depicts the chemical structure of naturally found xanthine derivatives.

Caffeine (**1**) (1, 3, 7- trimethylxanthine) is the more thoroughly studied natural xanthine alkaloid to date. It acts as a stimulant in humans and occurs naturally in beans, leaves, and fruit of more than 60 plants. It acts as a natural pesticide [37, 38, 39, 40, 41]. Caffeine acts as central nervous system (CNS) stimulator and plays important role in warding off drowsiness and restoring mental alertness, improves clear thinking and attenuated fatigue [6]. The presence of caffeine in beverages such as coffee, tea, chocolate, soft drinks and energy drinks, give it a popular recognition as world's most consumed psychoactive substance [42]. Caffeine is easily absorbed from the gastrointestinal tract [40]. The principle mode of action of caffeine is in antagonization of adenosine receptor and phosphodiesterase inhibition [43, 44]. Thus, reduction in adenosine activity leads to increase in activity of the neurotransmitter dopamine. Caffeine can enhance the stimulation of epinephrine, epinephrine-like drugs including amphetamine, methamphetamine, or methylphenidate, etc, by regulating the catalytic action cAMP-phosphodiesterase (cAMP-PDE) and thus it leads to make cAMP available for the messaging cascade for various cellular functions [45]. Caffeine increases the levels of serotonin which causes positive mood changes [46, 47]. Caffeine has received lots of attention from sport regulatory institutions and even its use has been regulated by International Olympic Committee [6, 48].

Theophylline (**2**) (1, 3- dimethylxanthine) is the second widely researched natural xanthine derivative after caffeine. Its natural sources are black tea and green tea. In 1888, theophylline was first time extracted from tea leaves by German biologist Albrecht Kossel. Clinical use of theophylline was taken up for treating asthma in the 1950s. Theophylline is known for its therapeutics importance. It is widely known for its pharmaceutically active properties such as diuretic, cardiac stimulator, smooth muscle relaxant, bronchodilator and CNS stimulator and stabilizer of the mast cells [49, 50, 51, 52, 53]. Adenosine- stimulated release of mediators from mast cells, neutrophil activation, induction of 1L-1β and 1L-1α, synthesis and release of tumour necrosis factor (TNF-α) and cytokine release from T-lymphocytes are inhibited by theophylline [54]. Theophylline possesses anti-inflammatory, anti-tumour, and immunomodulatory activities [55]. Theophylline has also been reported as potent inhibitor for regulating the catalytic activity of alkaline phosphatase (Al-P) [56, 57].

Theobromine (**3**) (3, 7-dimethylxanthine) is derived from *Theobroma*, the genus of the cacao tree [58, 59]. It is the primary alkaloid found in cocoa and chocolate. The presence of theobromine in chocolate is one of the important causes for mood-elevating effects. The natural sources of theobromine are cacao, lesser extent in tea and coffee, and as a human metabolite of caffeine. In therapeutics, it is used as a diuretic, vasodilator, a myocardial stimulant, antitussive, antiangiogenic and anti tumour agent [60, 61, 62, 63].

Paraxanthine (**4**) (1,7-diimethylxanthine) is a major metabolite obtained as a result of biotransformation of caffeine. In human, after intake, nearly 80% of caffeine is demethylated at the N_3 position to yield paraxanthine. It acts as a potent, antagonist of adenosine receptors A_1, A_{2A}, and A_{2B} [34, 64]. As a result, paraxanthine triggers an elevated diastolic blood pressure, stimulation of thermogenesis, and an increase in plasma epinephrine [34]. Furthermore, paraxanthine shows lipolytic properties and its presence in the blood causes an increase in concentration of serum free fatty acid. Paraxanthine, unlike caffeine, acts as an enzymatic effector of Na^+/K^+ATPase. Thus, it increases the transport of potassium ions into skeletal muscle tissue. Similarly, the compound also stimulates increase in calcium ion concentration in muscle [65].

2.2.2. Biotransformation

Biotransformation is a process of conversion of compounds from one form to another using biological system (such as bacteria, fungi and enzyme) [66]. It is a process of alteration in molecular and atomic form of compounds under enzyme catalytic action. Among natural xanthine derivatives caffeine is a major component for biotransformation into its different metabolites. In mammalian system, natural xanthine derivative caffeine is biotransformed in liver cells by the catalytic action of cytochrome P450 enzyme into three primary metabolites: paraxanthine (84%), theobromine (12%), and theophylline (4%) as shown in Fig. 3 [67,68]. The caffeine biotransformation in plant parts like coffee fruits and leaves proceeds via theobromine, theophylline, 3-methylxanthine, 7-methylxanthine, xanthine, allantoin, allantoic acid and urea [58, 69, 70, 71]. Likewise, biotransformation of caffeine is also carried out in various other systems such as microorganism including bacteria, fungi, nematodes etc. Biotransformation of caffeine produces theobromine and paraxanthine in bacterial systems whereas theophylline is produced by fungi [41, 72, 73, 74]. Knowing the pathway of the organism for complete metabolism, inhibitors can be used to block a particular step of the pathway to truncate the fermentation process at a desired time. This may help in accumulating the desired compounds. Biotransformation acts significantly in providing avenue for large scale synthesis of metabolites and their use in further drug development process [66]. Therefore, biotransformation may be a viable alternate method and an emerging field for attaining xanthine derivatives. It is cost-effective, non-hazardous, eco-friendly and less energy demanding process which utilizes the raw materials at lower investment costs [75].

2.2.3. Transmethylation

Another process for the formation xanthine derivatives naturally in plants is transmethylation process. In transmethylation process methyl transferase enzymes plays important role in transferring methyl groups for conversion of one form of xanthine or xanthine derivatives to another form. In plants, the main biosynthesis pathway of
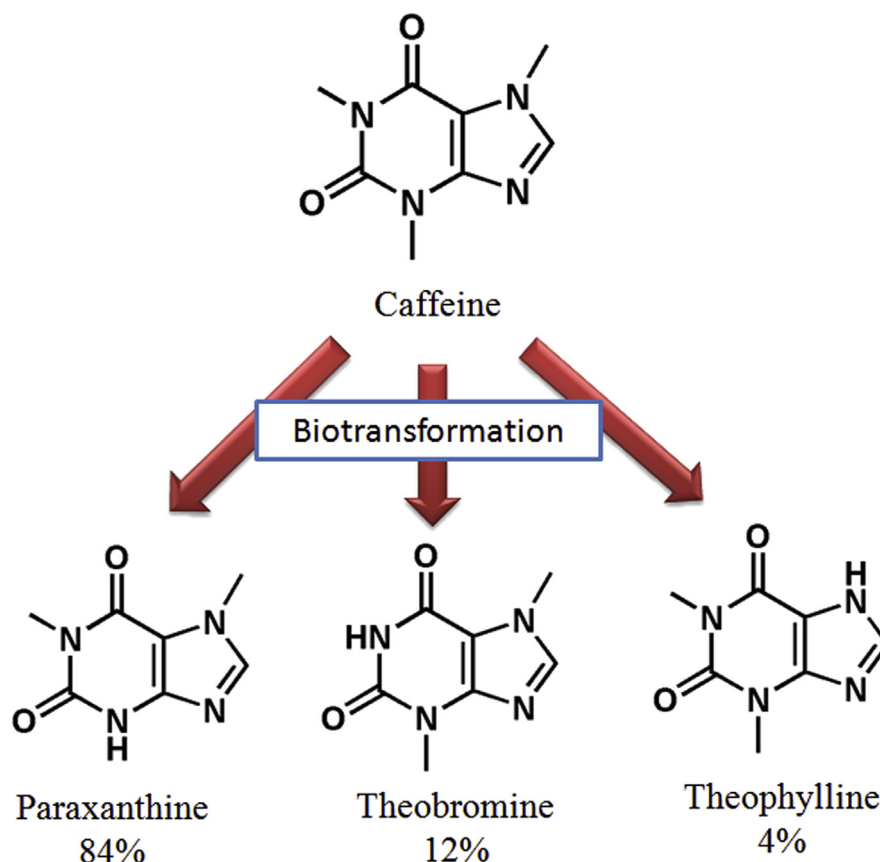
Fig. 3. Biotransformation of caffeine into other natural xanthine derivatives in mammalian system.

caffeine consists of four steps. Biosynthesis starts with xanthosine, a purine nucleotide which gives xanthine skeleton to caffeine. The biosynthesis process follows the sequence of xanthosine→ 7-methylxanthosine→ 7-methylxanthine→ theobromine→ caffeine [76]. The precursor molecule xanthosine is derived mainly from different pathways including de novo purine biosynthesis (de novo route), the degradation pathways of guanine nucleotides (GMP route) and adenine nucleotides (AMP route), and the S-adenosyl-L-methionine (SAM) cycle (SAM route) [76]. Xanthine is another precursor molecule for transmethylation. The transmethylation of xanthine in living system occurs in the sequence of xanthine→7-methylxanthine →3,7-dimethylxanthine (theobromine)→ caffeine [29]. Thus, transmethylation can be exploited as a process to develop methylated derivatives of precursor molecule. Using transmethylation process, obtained resultant derivatives can be used as starting materials for synthesis of various manually designed derivatives.

2.2.4. Chemical synthesis

Very few xanthine derivatives have been reported from plant and other natural sources. However, the pharmaceutical active nature of natural xanthine derivatives has

incentivized researchers to use these derivatives as lead molecule for synthesizing number of xanthine derivatives. Along with new xanthine derivatives, researchers have synthesized natural xanthine derivatives as well because their extraction from plant sources is uneconomical in large scale. For instance, the commercial availability of all methyl xanthines including theophylline is mostly through chemical synthesis. The commercial production of theophylline is commonly carried out by chemical synthesis which uses materials such as dimethyl urea and ethyl cyanoacetate [77]. Various methods have been reported for synthesis of xanthine derivatives. Ring closure mechanism, classical condensation and use of natural xanthine derivatives as starting material are some of them [12, 21, 22, 26, 28]. Traube synthesis mechanism is the widely used industrial method for synthesis in which 5, 6-diaminouracils formed from urea or N-substituted urea and followed by cyclization i,e. ring closure [11, 29, 78, 79]. Orthogonal safety-catch protection has been another strategy for synthesizing these derivatives [12, 80]. By using these schemes numbers of xanthine derivatives have been synthesized and used as therapeutics. Thus, chemical synthesis is a flexible route to escape complicated extraction methods from medicinal plants. However, this route has also many challenges that will be discussed in upcoming section. By bridging the existing lacuna, chemical synthesis can surely become a viable method for large scale diversification in derivatisation of xanthine derivatives.

2.2.5. Synthetic xanthine derivatives: an overview

With recognition of xanthine as a lead molecule in natural xanthine derivatives, it incentivized researchers to look at the derivatisation aspect to fetch more potent and selective compounds. Potency and selectivity of compounds towards their targets are imperative in drug development process. The structure of xanthine gives maximum possibility for diversification in derivatisation because of the presence of N^1, N^3, N^7 and C^8 positions for substitution. Fig. 4 illustrates the chemical structure of some of the key pharmaceutically active synthetically derived xanthine derivatives (**5−14**). Following paragraphs provide the description of existing known synthetically derived xanthine derivatives.

Aminophylline (**5**), a combination of theophylline and ethylenediamine in 2:1 ratio, is a bronchodilatating and antiasthmatic compound. Aminophylline have been widely used for the treatment of bronchial asthma, chronic obstructive pulmonary disease, and cardiovascular problems. It is commonly known as potent peripheral vasodilator [81, 82, 83]. Due to phosphodiesterase inhibitory properties aminophylline possess antioxidant effects in human neutrophils. Despite antioxidant properties, it generates sufficient amount of free radical which are the responsible factor for seizures inducing potential of aminophylline [83].

Another widely used xanthine derivative in therapeutics is IBMX (**7**) (1-Methyl-3-isobutylxanthine). It is a potent inhibitor of cyclic nucleotide phosphodiesterase. It
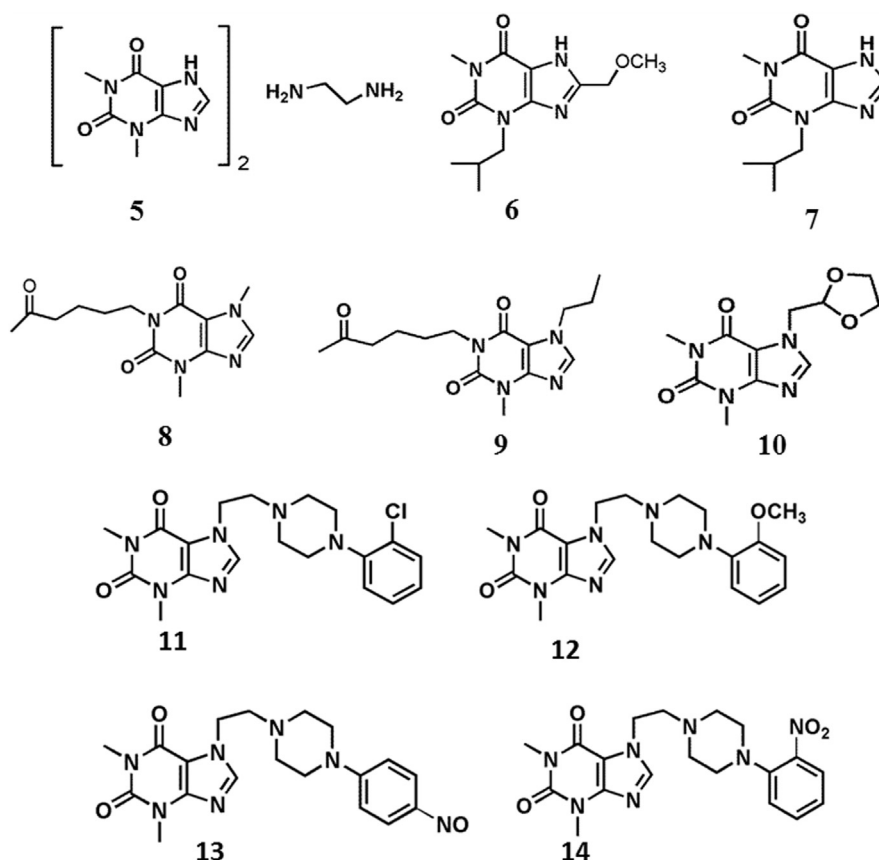
Fig. 4. Structure of synthetically derived xanthine derivatives.

increases cyclic AMP and cyclic GMP in tissue and thereby activates cyclic nucleotide-regulated protein kinases. IBMX acts as bronchodilator. IBMX non-specifically inhibits most of the phosphodiesterases except PDE9 and PDE8 [84, 85, 86]. It acts as calcium liberator by releasing calcium ions from Ca^{2+}-gated ion channels of neurons [87]. In HSP70-overexpressing cells, IBMX play imperative role in suppression of transcriptional activation of the tyrosinase gene [88] One similar xanthine derivative, 8-methoxymethyl-1-methyl-3- (2-methylpropyl) xanthine (**6**) specifically inhibits calmodulin-sensitive cGMP phosphodiesterase and it selectively inhibits Ca^{2+}/calmodulin-dependent phosphodiesterase [89, 90]. Thus IBMX and other similar derivatives are sometimes shows non-pharmaceutical properties because of their small size. Various researches have been aligned towards increasing size of xanthine derivatives to enhance the pharmaceutical properties.

The cellular and molecular effect of one another synthetically derived compound, pentoxifylline (**8**) is widely known in various pharmaceutical applications. It is a methyl xanthine derivative, which acts as haemorheological agent [91]. In the United States, pentoxifylline has been widely in use for the treatment of intermittent

claudication [91, 92]. It improves blood flow by decreasing its viscosity and increasing fibrinolytic activity in plasma. Thus, pentoxifylline is used for the treatment of peripheral vascular disease and cerebrovascular disease [93]. Pentoxifylline administration reduces peritoneal adhesion formation by altering peritoneal fibrinolytic activity [94]. Pentoxifylline has been found as a potent inhibitor of primary post-traumatic adhesion formation in a rodent model [95]. Thus, pentoxifylline has been widely used as safe, cost-effective therapeutic drug for various dermatological disease [96].

Propentofylline (**9**) (HWA285) is a unique xanthine derivative which exhibits various biochemical and pharmacological activities due to its neuroprotective, antioxidant and anti-inflammatory effects [97]. It acts as combined inhibitor of both adenosine transporter and phosphodiesterases. Propentofylline plays significant role in increasing the cerebral concentration of γ-aminobutyric acid (GABA) and adenosine while treating ischemia [98, 99]. It acts as neuroprotective glial cell modulator which suppresses the neurotoxic effects of microglial cells and thus restores the functions of astrocytes [100, 101]. It increases the blood flow in heart, brain and skeletal muscle [102]. Propentofylline has also been reported as a drug for significant protection from nerve cell damage which brain tumor, vascular dementia (VaD) and Alzheimer's disease (AD) [102, 103]. Thus wider mode of action, various biochemical and pharmaceutical activities make pentoxifylline a good drug for various therapeutic diseases.

In pharma, doxofylline (**10**) (7-(1,3-dioxalan-2-ylmethyl) theophylline), a 1,3,7-trisubstituted xanthine derivative has been proved as good therapeutic molecule. The mode of action of doxofylline differs with theophylline because of substitution at N_7 position with dioxalane group in molecular structure. Like theophylline it act as inhibitor for phosphodiesterase but it shows poor antagonist activities for adenosine A1 and A2 receptors [104]. Doxofylline may participate in reducing various side effects such as gastric acid secretion. This suggests that the drug can be used safely and effectively without encountering the side effect which most of the xanthine derivatives are facing while treating particular disease [105]. Additionally, doxofylline has been reported with various pharmacological effects such as anti-inflammatory and bronchodilator activities [106]. Thus, the administration of drug is safe and cost-effective with diminutive side effects.

Another group of compounds commonly known as, KMUPs are unique xanthine and piperazine derivative widely used pharmaceutically active compounds [107, 108, 109, 110, 111]. Till date four KMUP derivatives (KMUP-1 (**11**) (7-[2-[4-(2-chlorophenyl) piperazinyl]ethyl]-1,3-dimethylxanthine), KMUP-2 (**12**) (7-[2-[4-(2-methoxy) piperazinyl]ethyl]-1,3-dimethylxanthine), KMUP-3 (**13**) (7-[2-[4-(4-nitro) piperazinyl] ethyl]-1,3-dimethylxanthine) and KMUP-4 (**14**) (7-[2-[4-(2-nitro) piperazinyl] ethyl]-1,3-dimethylxanthine) are reported with their therapeutic activities. KMUP

derivatives, act as inhibitor for PDE3, PDE4 and PDE5 thus maintaining the level of second messengers which in turn activate protein kinase A (PKA), protein kinases G (PKG) and K^+ channels which results tracheal smooth muscle relaxation [19, 112, 113]. KMUP-1 and KMUP-3 acts as eNOS/cGMP-enhancer which increases the level of nitric oxide (NO), gaseous second messenger, through endothelium nitric-oxide synthase (eNOS) [109, 114, 115]. It plays significant role in increasing eNOS expression, inhibiting iNOS expression, and inhibiting pulmonary hypertension [116]. KMUP derivatives can attenuate isoprenaline-induced cardiac hypertrophy and inhibit right ventricular hypertrophy induced by pulmonary artery hypertension. Thus, KMUP derivatives have been known for their multifunctional roles which include anti-inflammatory, anti-proliferation, neuroprotective, cardioprotective, anti-osteoclastogenic and anti-resorptive activities [109, 113].

As seen from the above examples, xanthine as scaffold has given number of therapeutically active drug candidates. These molecules have been used mainly to treat diseases related to dysfunction of cellular signaling pathway by targeting key enzymes of pathway confirming the scope and potency of the xanthine scaffold.

2.3. Xanthine derivatives and their therapeutic avenues

In recent years, xanthine derivatives have brought various attentions because of their dietary effects and their wider natural presence. Various natural and synthetic xanthine derivatives have been recognized as therapeutically potent compounds and reported for targeting various diseases. In terms of potential health benefits, interests towards these compounds have been increasing from the scientific communities, industries and consumers. The following section of the review addresses the various diseases/pathophysiological conditions which have been attended by xanthine based molecules. Fig. 5 illustrates the therapeutic course of action of xanthine derivatives in different parts of human body.
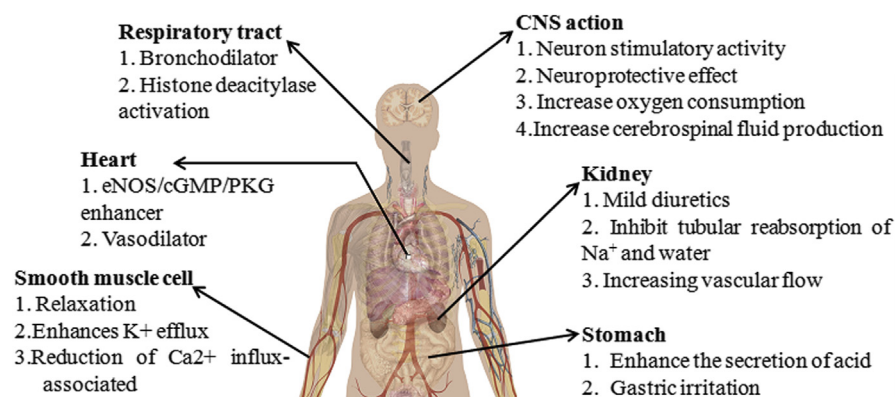
Fig. 5. Therapeutic disease targets of xanthine derivatives.

2.3.1. Respiratory tract diseases

For many years xanthine derivatives have been widely used for the treatment of respiratory diseases. They are best known for their bronchodilator action. Earlier in the 20th century theophylline was particularly used as bronchodilator but years later the aminophylline (combination of theophylline and ethylenediamine) and glycine theophyllinate were taken up as effective bronchodilator to treat acute asthma [117]. Since then several bronchodilators have been developed. Traditionally, xanthines derivatives such as caffeine, theobromine, theophylline aminophylline, diprophylline, acephylline piperazine, etophylline, proxyphylline, 3-isobutyl-1-methylxanthine, paraxanthine, pentoxifylline, etc., are reported for their bronchodilator activity for treating asthma [31, 118, 119]. One of the major reasons for respiratory tract diseases is reduction in activity of histone deacetylase (HDAC). Xanthine derivatives as caffeine and theophylline are reported for increasing the activation of HDAC [120, 121]. Hence, xanthine derivatives present in the coffee, cocoa are act as relief system in asthmatic patient.

2.3.2. Neurodegenerative disease

Neuro-stimulatory actions of caffeine are well-known [32]. Adenosine acts as modulator in various physiological and pathophysiological processes in central nervous system (CNS). The structural similarity of xanthine derivatives play imperative role in the blocking of adenosine receptors to maintain the concentration of extracellular adenosine, thus, make available signaling molecule for adenylate cyclase mediated heart cell signaling pathway. Propentofylline and KMUP-1 are widely used as neuro-protecting xanthine derivatives [111, 113, 122, 123, 124]. Likewise various other xanthine derivatives show neuroprotective effect because of their course of action as phosphodiesterase inhibitor, blocker of adenosine uptake in neuron and glial cells and antagonist of adenosine receptors [122, 123, 125, 126]. The neuro-active effect of xanthine derivatives increases the life of brain cells. Higher neural activity may lead to increased oxygen consumption and cerebrospinal fluid production in brain. Because of these reasons xanthine derivatives have been used for the treatment of various neurodegenerative disease including Alzheimer disease, Parkinson disease, ischemia, etc [32].

2.3.3. Hypertension and cardiovascular diseases

Xanthine derivatives have various effects in heart and blood vessels. Conventional xanthine derivatives such as caffeine, theophylline, theobromine and aminophylline are reported as vasodilators [32]. In a group of middle age population, cocoa drinks enriched with theobromine significantly increases the ambulatory systolic blood pressure within 24 hours while the central and peripheral systolic blood pressure come down to normal level after two hour of consumption [32]. Xanthine

derivatives are also reported as eNOS/cGMP/PKG enhancer. Endothelial nitric oxide synthase (eNOS) and inducible NOS (iNOS) are important enzymes play important role in production of nitric oxide (NO) and cyclic guanosine monophosphate (cGMP). NO and cGMP act as second messenger in heart cell signaling pathway. Xanthine derivatives increase the expression of eNOS and thus maintaining the appropriate level of second messengers for various heart cellular functioning. KMUP-1, a xanthine derivative, shows antihypertrophic effect to treat left ventricular hypertrophy (LVH) which develops due to cardiac stress [116]. Therefore, in cardiovascular diseases, xanthine derivatives effectively show therapeutics effect on blood pressure, arterial stiffness, circulating catecholamine, and endothelial dependent vasodilation [127].

2.3.4. Renal disease treatment

Natural xanthine derivatives such as caffeine and theophylline have been reported for treatment of renal disease since 1864. It is widely known that natural xanthine derivative have been used to increase urine output until the development of more potent diuretic [128]. The diuretic potency of natural xanthine derivatives are reported as theophylline > caffeine > paraxanthine > theobromine [128]. Though diuretic and natriuretic effect of natural xanthine derivatives are well established but the mechanism behind this activity is still not clear. A_1 receptor blockade by xanthine derivatives could be most probable reason for diuretic effect of these derivatives because they act as antagonist of adenosine which is key regulator of kidney function by regulating the level of glomerular filtration rate (GFR), medullary blood flow, and renal water and electrolyte transport. Here, xanthine derivatives act as A_1 receptor antagonists which increase renal fluid and Na^+ excretion by blocking the adenosine receptor. Therefore, diuresis and natriuresis has been observed primarily due to selective A1 receptor blockade which is caused by inhibition of renal reabsorption [129].

2.3.5. Smooth muscle relaxation

The phosphodiesterase inhibition properties of xanthine derivatives have been related to their tracheal relaxant activities [7, 33, 130]. Smooth muscle cell relaxation is carried out through the activation of Adenylyl cyclase (AC) and soluble Guanylyl cyclase (GC) which leads to synthesis of second messengers - cAMP and cGMP respectively. The level of these second messengers is regulated by cyclic nucleotide phosphodiesterases. The phosphodiesterase inhibitory action of xanthine derivatives leads to accumulation of cAMP/cGMP which further activates PKA/PKG and enhances K^+ efflux. It leads to reduction of Ca^{2+} influx-associated contractility in tracheal smooth muscle (TSM) [131]. KMUP-1, KMUP-3 and KMUP-4 are well studied smooth muscle relaxant [108, 112, 131].

2.3.6. Gastric acid secretion

Gastric distress is one of the most frequent side effects in course of treatment with xanthine derivatives. It has been reported that the xanthine derivative which are antagonist of adenosine are mostly responsible for gastric acid and pepsin secretion. Theophylline, aminophylline, caffeine etc come under this category because of their potency towards the adenosine receptor as antagonists [132]. However, xanthine derivatives such as doxofylline and enprofylline, are poor antagonist of adenosine and do not stimulate gastric acid and pepsin secretion [104, 132]. Doxofylline may participate in reducing various side effects such as gastric acid secretion. Thus, the administration of these selective drugs can make significant difference towards the specific target without encountering the side effect which are the most common issue with other xanthine derivatives facing while treating particular disease [105].

Thus, with creating difference towards the specificity for adenosine receptor, xanthine derivatives can be used as safer drug for various other targets such as PDE inhibition, anti tumor activity, anti-inflammatory activities etc.

2.4. Mechanism of action of xanthine derivatives in mammalian cells

Xanthine derivatives go through various regulatory courses of action insides the cellular system by targeting some of the important components of cell signaling such as Adenosine receptor antagonism, phosphodiesterase enzyme inhibition, and histone deacetylase activation.

2.4.1. Antagonizing activity for adenosine receptor

Adenosine is an endogenous nucleoside, an essential component for life dispersed in various mammalian tissues. It acts as a physiological regulator in variety of cellular signaling pathways and synaptic processes. It involves in multitudinous physiological functions including synthesis of nucleic acids, reduces tissue injury and promotes repair, control the level of neurotransmitters in the central nervous system (CNS), etc [133]. Multiple actions carried out by adenosine depend on the activation of adenosine receptors. In mammalian cells, four types of adenosine receptors A_1, A_3, A_{2A} and A_{2B} are reported. Adenosine and its agonist regulate the activity of adenylate cyclase by activation of all four adenosine receptor in which activation of A_1 and A_3 lead to G_i mediated inhibition of adenylate cyclase while activation of A_{2A} and A_{2B} lead to G_s mediated activation of adenylate cyclase as shown in Fig. 6. The activation of adenylate cyclase further leads to increase the concentration of cAMP, a second messenger plays vital role in various cellular functions [134]. In pathophysiological condition the activation of A_1 and A_3 receptors are detrimental for normal cellular functioning and can cause various diseases. The role of antagonist of
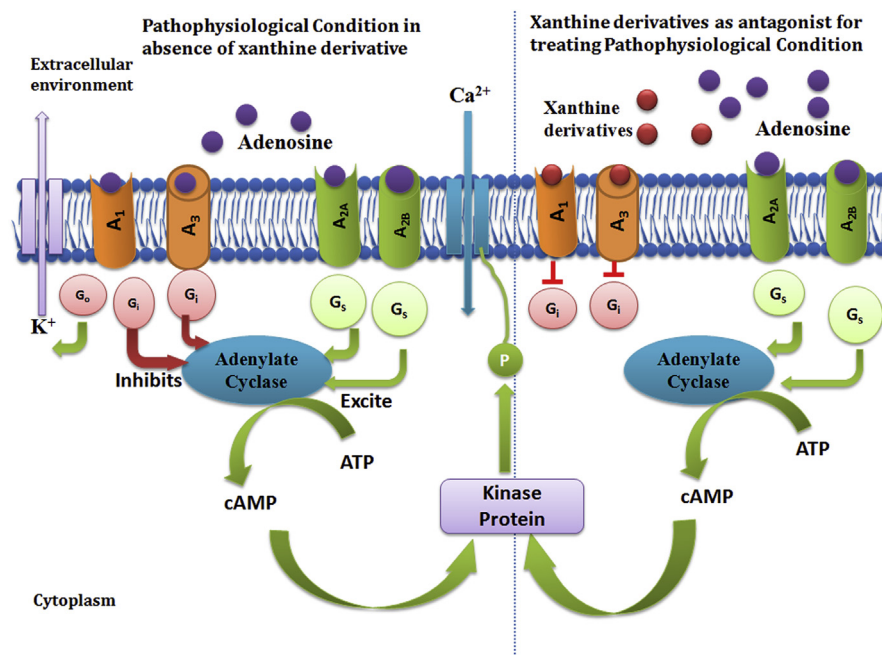
Fig. 6. Activation of adenosine receptors in normal physiological condition and role of xanthine as antagonist for adenosine receptor in pathophysiological condition to regulate the activation of adenosine receptor.

adenosine becomes essential to regulate the catalytic action of A_1 and A_3. Generally, over expression of A_{2A} and A_{2B} receptor causes various dysfunctions such as vasodilation, mast cell degranulation, chloride secretion in epithelial cells, smooth muscle contraction, increase cytokines, increase of glucose production, etc [21]. Hence, antagonist of A_{2A} and A_{2B} receptors are required to treat such situation. Due to structural similarity with adenosine, xanthine derivatives act as both agonist and antagonist on adenosine receptors [21, 135, 136]. Caffeine and theophylline are the earliest compounds indentified with antagonist activity for adenosine receptors but with moderate selectivity [32, 136, 137]. Thus, structural modification might have significant impact in improving the potency of xanthine derivatives towards adenosine receptors. Fig. 6 illustrates the mechanism of action of xanthine derivatives in cell signaling by antagonizing activity on adenosine receptors.

2.4.2. Phosphodiesterase inhibitory activity

In mammalian signal transduction pathways, second messengers play prominent role in processing the signals coming from the extracellular environment through membrane bound receptors for various cellular functions [138]. Cyclic nucleotides Phosphodiesterases (PDEs) regulate the level of second messengers - cAMP and/or cGMP and thus regulate the various cellular process. PDEs are superfamily of 11 enzymes (PDE1-11) encoded by 21 genes in human genome [139, 140, 141, 142, 143]. In normal physiological condition, regular functioning of PDEs are required

to maintain appropriate level of cAMP or/and cGMP which act as mediator to process the signals for various cellular functions. In various pathophysiological conditions, the level of second messengers lowered either due to dysfunction of receptor protein or due to low level of available signals. In such situation regular functioning of PDEs further decreases the level of cAMP or/and cGMP. All these in turn may affect the normal functioning of pathway [144, 145]. Here, inhibitor plays imperative role in regulating the catalytic action of PDEs [145]. Xanthine derivatives are known for their phosphodiesterase inhibition but most of these inhibitions are non-specific [7, 84, 85]. Theophylline shows bronchodilator effects, because of its ability to inhibit phosphodiesterase (PDEs) [51, 146]. Theophylline has been shown to inhibit tissue growth factor β (TGF-β) mediated conversion of pulmonary fibroblasts into myofibroblasts in COPD and asthma patients via cAMP-PKA pathway and suppresses COL1 mRNA, which codes for the protein collagen [147]. Fig. 7 depicts the role of xanthine derivatives in regulating the catalytic action of phosphodiesterases in pathophysiological condition to maintain the level of second messengers for maintaining the consistency in signal transduction pathway.

2.4.3. Histone deacetylase activation

Histone deacetylase (HDAC) is an important enzyme that regulates the chromatin structure and thus affects inflammatory gene expression [120]. Acetylation and deacetylation of histone is important phenomenon for transcriptional activation and repression, respectively, of inflammatory gene expression. Histone deacetylase (HDAC) acts as repressor for activation of inflammatory genes. The activation of
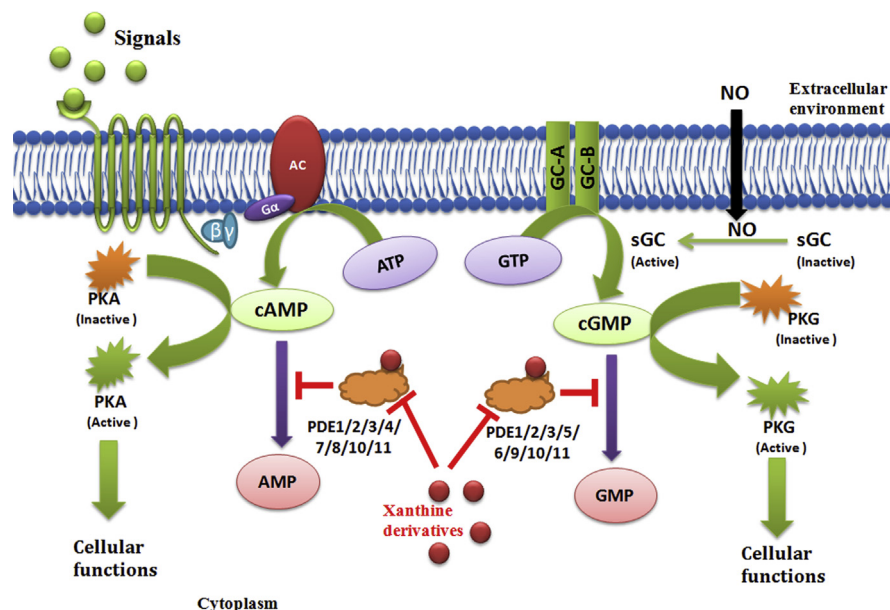
Fig. 7. Action of xanthine derivatives as inhibitor for regulating the catalytic action of PDEs in signal transduction pathway.

histone deacetylase depends on the level of glucocorticoids which is received by glucocorticoid receptor (GR). In cigarette smokers, due to oxidative stress, the glucocorticoid level reduces that leads to reduction in HDAC activity. Thus, in absence of HDAC activity, expression of inflammatory gene increases. Theophylline and other xanthine derivatives act as stimulator of HDAC activation [120, 121]. The activation of HDAC by xanthine derivatives shows their potential to act as novel anti-asthmatic drug. Thereafter, the activated HDAC are subsequently used to suppress inflammatory genes [120, 121].

Thus, targeting cell signaling pathway by different course of action ensures the multiple roles of xanthine derivatives inside the body which increases the potential of the xanthine as scaffold for future drug development.

2.5. Role of xanthine derivatives in pharmacology

For development of promising future drug candidates using the xanthine scaffold, pharmaceutical property analysis of existing drugs constructed over the same scaffold becomes imperative. This will ensure the suitability of constructing future drug candidates in the same line using the same scaffold. Antimicrobial, anti-inflammatory, anti-tumor, antioxidant properties are some of the important parameters to ensure the pharmaceutical properties of existing xanthine derivatives.

2.5.1. Antimicrobial activities of xanthine derivatives

In drug development process, antimicrobial activity of drugs becomes imperative to effectively combat microbial resistance. Xanthine derivatives such as caffeine, theophylline, aminophylline, pentoxifylline are reported for their antimicrobial effects as bactericidal, fungicidal and nematocidal [12, 148]. Caffeine is reported for enhancing the inhibitory effect of existing antibacterial agents such as Penicillin and tetracycline against *Staphylococcus aureus* [148]. Besides that, antimicrobial properties of caffeine have been reported against: human pathogens like *Klebsiella pneumonia*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* [39]. For caffeine, the minimum inhibitory concentration (MIC) for the above mentioned microorganisms are reported between 5 to 20 mM whereas minimum bactericidal concentration (MBC) have been reported in range from 43 to 100 mM, respectively [39]. These derivatives act as antimicrobial agent through the action of nucleic acid synthesis [22]. It is reported bacterial infection may lead to asthma pathogenesis. Some derivatives are best known for treatment of asthma because of their antimicrobial action [22].

2.5.2. Anti inflammatory activities of xanthine derivatives

There are increasing evidence that xanthine derivatives such as caffeine, theophylline, pentoxifylline, KMUP-1, etc show anti-inflammatory effect [19]. Anti-

inflammatory responses of these derivatives are the result of their non-selective phosphodiesterase inhibition and/or their non-selective adenosine receptor antagonist properties. PDE inhibition and/or adenosine antagonist role of xanthine derivatives leads to increase in cAMP concentration, activation of protein kinase A, inhibition of tumor necrosis factor (TNF-α) and leukotriene synthesis. With inhibition of leukotrienes synthesis, inflammation reduces [19, 31]. Leukotrienes increase inflammation by raising leukocyte infiltration, phagocyte microbial ingestion, and generation of pro-inflammatory cytokines such as IL-5, TNFα, and macrophage inflammatory protein-1β [31]. Pentoxifylline is one of the most used xanthine derivatives with anti-inflammatory effect by inhibiting the production of TNFα, therefore it has been found effective in both dermatological as well as non-dermatological conditions [96]. In patient with COPD, xanthine derivatives such as caffeine, theophylline, etc are reported for their effective role in reduction of leukotriene synthesis by reducing the proportion of neutrophils [31, 149].

2.5.3. Anti-oxidant activity of xanthine derivatives

There are various reports which say pathological changes may occur due to excessive accumulation of oxygen and nitrogen reaction product in body fluids including free radicals such as reactive oxygen species (ROS) and nitric oxide (NO) [150]. These changes may cause premature aging. ROS act as mediator in various cellular signaling pathways. The hyperproduction of ROS is limited by both enzymatic mechanisms and natural antioxidants such as uric acid, glutathione, vitamin C and E [150]. In the lack of appropriate regulation the level of ROS increases and leads to oxidative and nitrosative stresses. Thus, xanthine derivatives such as caffeine, theophylline, theobromine, etc, have been reported for their antioxidant activities [150, 151, 152].

2.5.4. Anti-tumour activities of xanthine derivatives

Several xanthine derivatives are reported for their inhibitory affinity of cell transformation. In lower eukaryotes and bacteria, these compounds induce gene mutations. They act as an antagonist of adenosine receptor and exert antiangiogenic properties in many types of tumors including ovarian cancer cells, prostate cancer [60, 61]. Xanthine derivatives such as caffeine, theophylline, pentoxifylline, theobromine, etc, are reported for inhibition of adriamycin and doxorubicin efflux from tumor cells. This inhibition leads to increase in concentration of doxorubicin in tumor enhancing anti tumor activity of doxorubicin [62, 153, 154, 155].xz.

Thus, by targeting the above key cellular mechanism, these derivatives help to reduce the mortality and morbidity rate significantly.

2.6. Pharmacokinetics of xanthines derivatives

Pharmacokinetics of therapeutic drug is imperative to ensure the safe and effective management of the drug molecule inside the body. Physiochemical parameters such as water solubility and lipid solubility may cause change in the pharmacokinetic parameters such as rate of absorption, distribution, metabolism, transport, excretion, therapeutic plasma level etc. With change in structure through substitution at different positions of xanthine changes the metabolic rate of xanthine derivatives. For instance, synthetic xanthine derivative pentoxifylline, is metabolized through its oxohexyl side chain. Whereas, in case of natural xanthine derivatives such as caffeine, theophylline, theobromine etc, metabolization is carried out via demethylation reaction. Pentoxifylline with polar oxohexyl side chain substitution at N^1 position provides better tolerant potential than natural xanthine derivatives because demethylase enzymes do not break its N^1 substituent [156]. Water solubility and partition co-efficient have been very important parameters for resorption and desorption in body. For many years n-octanol-water partition system has been satisfactory for comparing lipid solubility with biological distribution. Natural xanthine derivatives such as caffeine, theophylline, theobromine etc are with poor water solubility. One of the most important reason for such poor solubility is their strong inter-base hydrogen bond and base stacking [157]. Another important factor for poor solubility of xanthine derivate is existence of strong intra-molecular bond between N-H-groups [158]. It has been reported that the solubility of the natural derivatives improves in complexes. For instance, aminophylline (i.e. complex of theophylline and ethylenediamine) shows better solubility than theophylline [159]. Similarly, salts like choline theophyllinate or oxtriphylline possess better solubility. Substitution at different position of xanthine causes different potency. Along with potency substitutions also affect the physiochemical properties of compounds such as water solubility, metabolic rate, distribution and excretion [160]. Hydrophobic substituent at C^8 position has been reported for increasing potency towards adenosine receptor as well as phosphodiesterase inhibition because of establishing the strong hydrophobic interaction with the target but these changes decrease water solubility [137].

2.7. Biological implications of different substitution sites of xanthine

As Xanthine provides maximum possibility of substitution, Fig. 8 illustrates the pharmacological importance of different substitutions sites of the xanthine scaffold. Most of the substituted xanthine derivatives are reported as pharmacologically active compounds with well-known activity as adenosine receptor antagonists, phosphodiesterase inhibitors, cystic fibrosis transmembrane conductance Regulator (CFTR) activation and inducers of histone deacetylase activity [12, 120, 121, 161]. From the various in vitro analyses of natural xanthine derivatives such as theophylline,
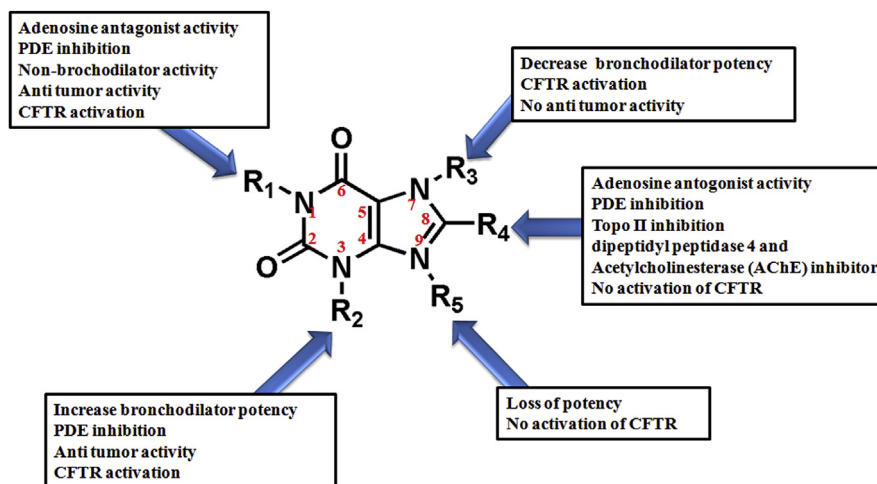
Fig. 8. Pharmaceutical significance of different substitution sites of xanthine scaffold to generate specificity and potency in drug development.

theobromine and caffeine it was found that N^3 substitution has important role in generating bronchodilator properties of compounds [162]. N^1 substitution of xanthine generates adenosine antagonism properties [162]. But N^1 substitution along with N^3 substitution further enhances the potency towards adenosine receptor. N^7 substitution shows mixed impact. N^7 substituted xanthine derivatives such as caffeine, theobromine, diprophylline, acephylline piperazine, etophylline and proxyphylline are reported for their bronchodilator activity [118, 119]. Though N^7 substitution increases bronchoselectivity but it decreases the adenosine receptor affinity [137, 163]. Due to presence of methyl group at N^7 position of caffeine, it is threefold less potent than theophylline towards adenosine receptor. Therefore, in most cases bulkiness of N^7-substituents considerably decreases the affinity [137, 164]. With comparative studies of different substituent at different sites of xanthine it was found that N^7 substitution shows comparatively lower potency as bronchodilator than C^8 substituted compounds [119]. The C^8 substitution has significant impact in increasing the pharmaceutical properties of compounds. The combined substitution at C^8 position with N^1 and N^3 positions of xanthine are reported with better potency and anti allergic properties [165]. N^1, N^3 and C^8 substitutions together are most promising sites of substitution on xanthine scaffold for generating compounds with selective potency towards subtypes of adenosine receptors [166]. Along with adenosine antagonist, xanthine derivatives with C^8 substitution are also reported as PDE inhibitor, Topo II inhibitor, dipeptidyl peptidase 4 and acetylcholinesterase (AChE) inhibitor [34, 167, 168]. Aryl substitution at C^8 position show immense affinity for increasing the inhibition potential of compounds towards PDEs as well as adenosine receptors. It is evident from the comparative studies of theophylline and C^8 substituted 8-phenyl theophylline where 8-phenyl theophylline shows 100- and 30-fold more potency towards A1 and A2 receptors, respectively [137]. Increasing

chain length at N^1 and N^3 site of xanthine increases the potency of compounds towards adenosine receptor and PDEs [137]. Substitution with alkyl groups at N^1, N^3 and N^7 positions of xanthine are crucial for activation of CFTR. However, substitution at C^8 and N^9 positions does not activate CFTR. Thus, by manipulating C^8 position of compounds, they can be made selective towards adenosine receptor. N^7 position may activate CFTR except when N^1 and N^3 positions are occupied with methyl group [161]. The xanthine derivatives at N^1 and N^3 position with alkyl substitutions are reported for their antitumor activities. Here also N^7 substitutions are reported with mixed response. Some cases of N^7 substitution shows inhibitory affinity of cell transformation, however, most of the time N^7 substitution has been non influential on cellular viability [169]. N^3 substitution with increased alkyl chain length is more effective for inhibition of cell transformation [169]. Substitution at N^9 position generally losses the bronchodilator potency of xanthine derivatives as well as substitution at this position does not activate CFTR [161].

The basic structure of xanthine consists two rings- one ring is of six membered pyrimidinedione ring and second ring is of five membered imidazole ring. Xanthine basic structure itself has significance in generating pharmaceutically active nature. It was evident by studies on alternation of basic structure of xanthine ring including enlargement of xanthine ring, insertion of additional benzene ring, hybridization of xanthine with adenosine and synthesizing mesoionic derivatives of xanthine [15, 137, 170, 171]. Alternation in xanthine basic structure leads to decrease in biological potency. Enlargement of six-membered pyrimidinedione ring of xanthine to a seven-membered diazepinedione ring leads to weaker interaction with adenosine receptor. This was mainly because the enlarged ring system loss planarity [137, 172]. Thus, along with different substitution site basic structure of xanthine itself has significant role in generating biological potency towards the target.

2.8. Lacuna in the current synthesis methods of xanthine derivatives

Most of the earlier studies have used the ring closure synthetic route and classical condensation route for the synthesis of the xanthine derivatives [12, 21, 26]. The existing schemes are endured with several bottlenecks, such as use of toxic and expensive reagents/catalysts, use of acid/base or external oxidant, isolation of imine intermediate, high temperature, hazardous solvents, lengthened reaction time, tedious workup, by-products formation, low yields, expensive chemicals etc [25, 26, 173]. Use of existing xanthine based molecules (such as theophylline, caffeine, theobromine, IBMX etc) as reaction initiator has been reported as another widely used synthetic approach for the synthesis of new xanthine derivatives [24, 25, 27]. But in these derivatives, the availability of limited sites for substitution is the major issue. For instance, in case of theobromine, N^3 and N^7 positions are already

occupied by methyl groups. Thus, only N^1 and C^8 positions are available for substitution [25]. Therefore, the existing methods are not favorable for the synthesis of large number of diverse xanthine derivatives.

2.9. Scope for molecular diversification using xanthine as scaffold in future drug development

Despite enormous ground available for substitution/modification still use of xanthine is limited in drug development process. Till date no research has been carried out using xanthine as starting material for xanthine derivatives. This is mainly because of the lack of proper understanding of the structural nature of xanthine. According to reports available till date, N^3 position of xanthine has been considered as most reactive in xanthine and substitution follows the −NH group of $N^3 > N^7 > N^1$ positions [29]. This analysis was contradictory to the transmethylation process of xanthine in living organism. The transmethylation of xanthine occurs in sequence of $N^7 > N^3 > N^1$ i.e. xanthine→7-methylxanthine→3,7-dimethylxanthine (theobromine)→1,3,7-trimethylxanthine (caffeine) [29]. Thus, with considering N^3 position most reactive site among all −NH groups on xanthine, most of the reports initiated synthesis with substitution at N^3 position. However, this substitution was not directly carried out on the xanthine scaffold. N_3 substitution in most of the reports starts with cyclization/condensation of substituted urea and this process is commonly known as ring closure mechanism and classical condensation process [174, 175]. In our research analysis we have found that the synthetic substitution process undoubtedly follows the natural transmethylation sequences i.e. $N^7 > N^3 > N^1$ [data not published]. The reactivity difference is due to different atomic environment of three −NH groups. Among three −NH groups, −NH at N^7 position faces less steric hinderance than other two −NH positions whereas −NH at N^1 position faces highest steric hinderance. Therefore, based on the reactivity pattern, substitution follows the same order as it is found in living system i.e. $N^7 > N^3 > N^1$. Therefore, by selective sequential substitution in order of $N^7 > N^3 > N^1$, numbers of derivatives can be synthesized. The presence of three −NH groups makes the xanthine highly polar compound and that also could be a major reason for not using xanthine for synthesis of xanthine derivatives because separation of reaction product become difficult through column chromatography and also it becomes time consuming process with heavy use of costly solvents and end product obtained with less yield. To overcome this technical difficulty, concentration optimization of reactants can be a good way to achieve target substitution. The selective substitution can also be achieved by protecting higher reactive site if that site is not chosen for substitution. Using xanthine as starting material for synthesis would be cost effective, time saving, non-hazardous, less tedious and high yield producing because there would be no need to give extra effort for cyclization of xanthine ring. Abundance of xanthine naturally makes it a better alternative of any existing starting
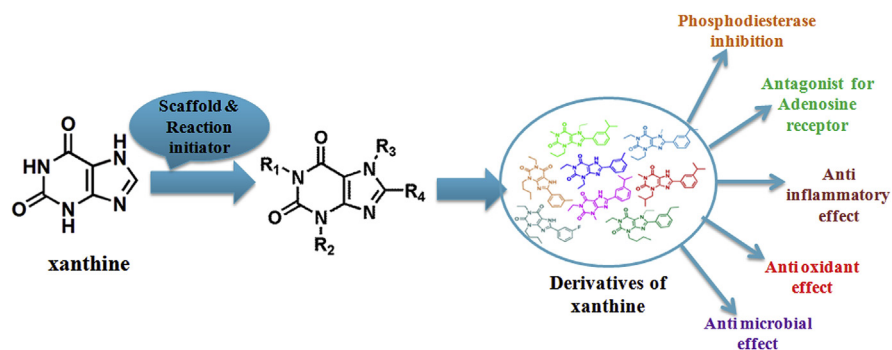
Fig. 9. Xanthine as a lead molecule for future drugs for several therapeutic targets.

material. Thus, with considering the huge potential of xanthine in maximizing the derivatisation with structural diversification, it can become an ideal choice as 'reaction initiator' for future xanthine based drug developments. Fig. 9 summarizes the potentiality of xanthine as a prospective lead molecule for future drugs.

3. Conclusions

Xanthine derivatives are best known for their course of action by targeting regulatory enzymes of cell signaling pathway through various pharmaceutical applications such as phosphodiesterase inhibition, adenosine antagonizing activity, activation of histone deacetylase, etc. This review has covered the routes for availability of xanthine derivatives, their structural details, therapeutic disease targets, mechanism of action, implication of different substitution sites, current lacuna in xanthine based drug development process along with future perspectives for the development of viable synthesis method. By going through therapeutic importance and different course of action of existing xanthine derivatives, this review has also tried to resolve the existing challenges in this field of research. The availability of xanthines from various routes such as natural source, biotransformation, transmethylation and chemical synthesis; have been brought out with their corresponding advantages and challenges. Chemical synthesis is one of the most promising ways to synthesize diversity of compounds using any fragment of interest. But this is the most challenging route among all. Available synthesis routes are unable to deliver large scale diversity in derivatisation. The present review has tried to explore the possibility of xanthine to act as starting material for large scale diversification in derivatisation reaction because of the availability of all sites (N^1, N^3, N^7, N^9 and C^8 sites) for the substitution. However, the presence of three $-NH$ groups has been the most challenging part in xanthine based drug development process. Thus, clear understanding over the reactivity pattern of different $-NH$ sites of xanthine is key to fetch full potential of xanthine in combinatorial drug development process. Thus, the subsequent understanding over the molecular and physiological behaviour of xanthine will be helpful in further research.

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Author contribution statement

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