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# Epigenetic impact of curcumin on stroke prevention

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**Abstract** The epigenetic impact of curcumin in stroke and neurodegenerative disorders is curiosity-arousing. It is derived from *Curcuma longa* (spice), possesses anti-oxidative, anti-inflammatory, anti-lipidemic, neuro-protective and recently shown to exhibit epigenetic modulatory properties. Epigenetic studies include DNA methylation, histone modifications and RNA-based mechanisms which regulate gene expression without altering nucleotide sequences. Curcumin has been shown to affect cancer by altering epigenetic changes but its role as an epigenetic agent in cerebral stroke has not been much explored. Although curcumin possesses remarkable medicinal properties, the bioavailability of curcumin has limited its success in epigenetic studies and clinical trials. The present review is therefore designed to look into epigenetic mechanisms that could be induced with curcumin during stroke, along with its molecular designing with different moieties that may increase its bioavailability. Curcumin has been shown to be encapsulated in exosomes, nano-vesicles (<200 nm), thereby showing its therapeutic effects in brain diseases. Curcumin delivered through nanoparticles has been shown to be neuroregenerative but the use of nanoparticles in brain has limitations. Hence, curcumin-encapsulated exosomes along with curcumin-primed exosomes (exosomes released by curcumin-treated cells) are much needed to be explored to broadly look into their use as a novel therapy for stroke.

**Keywords** Exosomes · DNA methylation · Histone modifications · microRNA · Oxidative stress

## Introduction

Cerebral stroke or “brain attack” is caused by interruption of blood supply to the brain which leads to the loss of brain functions (Langhorne et al. 2013). Cerebral stroke can be classified into ischemic (blockage of blood supply) or hemorrhagic (bursting of blood vessels). Thrombolytic agents, anti-platelet drugs, and neuro-surgery are the only available options for the treatment of stroke (Adams et al. 2007); however the protective therapy against cerebral stroke is yet to be discovered. Dietary components have found to exert immense impacts on normal functioning of the brain (Alamy and Bengelloun 2012; Bedi 2003; Gomez-Pinilla 2008) and contribute to the prevention of a series of brain diseases including stroke (Psaltopoulou et al. 2013). Reports indicate that dietary components not only evoke genetic, but also epigenetic components to compensate stroke, or stroke-like pathologies (Gallou-Kabani et al. 2007; Kalani et al. 2014a). In that regard the potential of curcumin, which also exhibits genetic and epigenetic influences, cannot be ignored. Curcumin is derived from the roots of *Curcumin longa* and due to remarkable medicinal properties; curcumin (diferuloylmethane) is termed as yellow gold. Curcumin treatment provides vascular protective effects in persons at risk for stroke (Ovbiagele 2008). The stroke preventive properties of curcumin can be attributed to: 1) neuro-protection via free radical scavenging, inhibiting nitric oxide synthase and lipid peroxidation (Strimpakos and Sharma 2008); 2) anti-inflammatory property by suppressing the production of IL-1, IL-8 and TNF- $\alpha$  (Strimpakos and Sharma 2008); 3) anti-lipidemic property by lowering cholesterol and boosting up HDL (Soni and Kuttan 1992) and; 4) anti-aggregation property by inhibiting platelet aggregation

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and inducing platelet aggregation factor (Strimpakos and Sharma 2008). The ability of curcumin to cross blood–brain-barrier (BBB) also favors its selection over other therapeutic agents/molecules during cerebral stroke (Mishra and Palanivelu 2008; Tsai et al. 2011). In addition, curcumin appears to have potential to inhibit amyloid beta oligomers and fibrils formation in mice (Yang et al. 2005). The therapeutic efficacy of curcumin in middle cerebral artery occlusion (MCAO) models of rat and mice has also been explored (Lapchak et al. 2011; Shukla et al. 2008; Tyagi et al. 2012; Zhao et al. 2010). Studies suggest that curcumin overcomes cerebral ischemia by its neuro-protective and anti-oxidative properties (Strimpakos and Sharma 2008; Tyagi et al. 2012). Besides exhibiting anti-inflammatory, anti-lipidemic, and anti-oxidative properties, curcumin also induces signs of epigenetic changes (Chiu et al. 2013; Hardy and Tollefsbol 2011; Martin et al. 2013; Teiten et al. 2013); however the epigenetic influence of curcumin on stroke epigenetics is needed to be explored. In this present review, we propose that curcumin affects molecular processes such as DNA methylation, histone modification, nucleosome remodeling, and small noncoding RNAs (ncRNAs) (e.g., miRNAs) that modulate gene expression and impart an important role in amelioration of stroke pathogenesis.

Since, curcumin possesses potential therapeutic effects, it has been recommended for clinical trials to prevent/treat brain disease, including stroke (Goel and Aggarwal 2010; Ovbiagele 2008; Perry and Howes 2011). Phase I clinical trials on curcumin were not successful due to its low bioavailability (Anand et al. 2007). The factors that limit curcumin bioavailability include; poor absorption, quick metabolism, and rapid systemic elimination. However, recent studies suggest that curcumin-encapsulated exosomes are more stable, highly soluble, highly concentrated in the blood and possess therapeutic potentials (Sun et al. 2010; Zhuang et al. 2011). Exosomes are the nano-vesicles (<200 nm) derived from the fusion of multivesicular body to the plasma membrane and found in the extracellular body fluids (serum, plasma, saliva, urine, breast milk, broncho-alveoli lavage) including culture conditioned media (Kalani et al. 2014b; They et al. 2002, 2006). These nano-units have been employed for the treatment of stroke in rat (Xin et al. 2013). Targeted delivery of curcumin-encapsulated exosomes to the brain through intranasal routes has been shown to be effective for brain inflammatory diseases (Zhuang et al. 2011). Interestingly, preliminary studies from our lab explored that curcumin-primed exosomes (CUR-EXO), derived from culture conditioned media of mouse brain endothelial cells (MBEC) treated with curcumin, might equally benefit since these units alleviate tight junction proteins and endothelial cell layer permeability in MBECs (unpublished data). These results concomitantly show the therapeutic aspects in CUR-primed, or CUR-encapsulated exosomes and provide a promising area

to explore their potentials to recover cerebral ischemic stroke probably by amelioration of epigenetic and molecular events.

Hence, the present review suggests the possible epigenetic mechanisms induced with curcumin along with a short discussion on molecular designing to enhance its bioavailability and impacts of curcumin encapsulated/curcumin-primed exosomes on stroke therapy.

### Epigenetic impact of curcumin

Fu et al. have suggested that curcumin may exert its biological activities through epigenetic modulation, even at lower concentrations (Fu and Kurzrock 2010). Epigenetic mechanisms regulate functional gene environment by regulating gene expressions without altering gene sequence or structure. The normal genetic expressions are under the control of various mechanisms such as: DNA methylation, histone modifications, non-coding small RNA (microRNA, miR), and RNA editing (Kalani et al. 2013; Qureshi and Mehler 2010b, 2012). These associated mechanisms may play immense role in normal physiological functions of the brain. Curcumin as an epigenetic agent can be used for stroke protection and therapeutics by reversing erroneous epigenetic alterations or inducing/controlling normal epigenetic mechanisms.

#### Role of curcumin in DNA methylation

DNA methylation is the transfer of methyl ( $-CH_3$ ) group from an activated donor (*s-adenosylmethionine*, SAM) to the cytosine residue of the specific region of the gene by the enzyme DNA methyltransferases (DNMTs) (Qureshi and Mehler 2010a). DNMTs play a profound role in DNA methylation and classified mainly as DNMT-1 (maintains methylation) and DNMT-3a, 3b (de-novo methylation). Studies suggest that abnormal methylation is linked to various diseases such as: cancer, atherosclerosis, auto-immunity and obesity (Novik et al. 2002). These regulators are the pivotal part of folate cycle, connected to homocysteine (Hcy) metabolism pathway (Kalani et al. 2013). The potentials of curcumin as an epigenetic agent have been explored by molecular docking studies done for the interaction of curcumin with DNMT-1. This study suggests that curcumin covalently blocks the catalytic thiolate of DNMT1 with an  $IC_{50}$  of 30 nM after 72 h of its treatment and it leads to an inhibitory effect on DNA methylation (Liu et al. 2009). One of the studies reported the use of curcumin at 5  $\mu$ M concentration that reverses promoter CpG methylation of *Neurog1*, a cancer marker and known to be highly methylated in cancer (Shu et al. 2011). The high methylation interrupted the expression of *Neurog1* in human prostate cancer LNCaP cells. These studies suggest the potential role of curcumin by DNMT inhibition. Curcuminoids,

which are stable derivatives of curcumin, are prepared for the formulation of different drugs and formed by adding different chemical groups to the curcumin to make it more soluble. Among different curcuminoids, demethoxycurcumin and bis-demethoxycurcumin have been reported to influence epigenetic properties (Liu et al. 2011). Curcuminoids have also been found to induce hypomethylation of miR203 promoter in bladder cancer cell (Saini et al. 2011). Although much studies report curcumin in cancer epigenetics by mitigating DNA methylation errors, the reports are lacking that explore and prove epigenetic impact of curcumin in stroke by improving the DNA methylation. Hence, epigenetic impact of curcumin in stroke can further be explored by directing the research towards cerebral stroke area (Fig. 1).

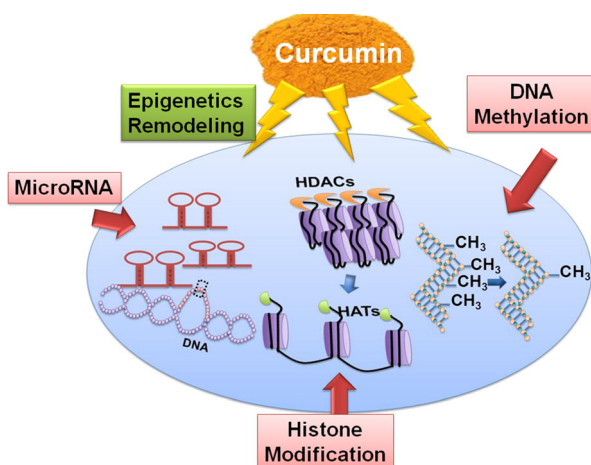
### Role of curcumin in histone modification

Histone modification is another important mechanism that regulates epigenetic events. Apoptotic and necrotic processes affect chromatin integrity and collectively progress neuronal injury in stroke. Histone modifications turn on or repress transcriptional processes that control gene regulations. Histone proteins (H2A, H2B, H3, and H4) along with linker DNA (H1) form a complex around which the DNA wraps to form nucleosome which is the basic unit of chromatin. Histone acetyltransferases (HATs) and histone deacetylases (HDACs) are the enzymes which control histone modifications by activation or repression of transcriptional machinery and chromatin remodeling (Kalani et al. 2013). Histone modification machinery also affects chromatin structurally and functionally by different processes such as; acetylation, methylation, phosphorylation, ubiquitination, and adenosine diphosphate ribosylation. Curcumin along with Trichostatin A, suberoylanilide hydroxamic acid, sodium butyrate, sodium

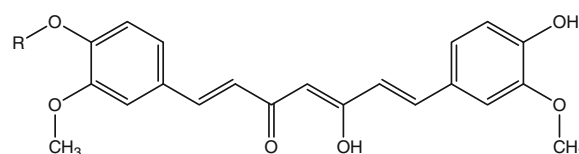
4-phenylbutyrate, valproic acid, and resveratrol have been reported as potential HDAC inhibitor (Kalani et al. 2013; Qureshi and Mehler 2011).

Recent report demonstrated the expression patterns of HDAC isoforms during experimental ischemia stroke. This study described HDAC-3 and HDAC-6 as potential mediators of the neurotoxicity during ischemia stroke and suggested specific therapeutic approach according to HDAC subtype (Chen et al. 2012). Inhibition of zinc dependent histone deacetylases is also reported to protect neurons, axons and associated glia cells from oxygen and glucose deprivation (Baltan et al. 2013). The beneficial effect of HDAC inhibitors as a therapeutic strategy was also proved by Baltan et al. (2013). The study showed that HDAC inhibition mechanism perpetuates through targeting mitochondrial energy regulation and excitotoxicity in ischemic white matter injury (Baltan et al. 2011). Collectively, earlier reports indicate that HDAC inhibition alleviates stroke-related pathology including functional and behavioral recovery. The associated mechanisms could be up-regulation of extracellular glutamate clearance, inhibition of p53-mediated cell death and maintenance of mitochondrial integrity (Baltan et al. 2013; Kim et al. 2007).

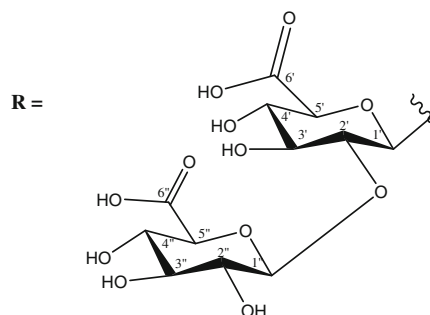
The potential of curcumin as HDAC inhibitor was also proven by molecular docking assay carried out for the human HDAC-8 enzyme in order to predict inhibition activity and the 3D poses of inhibitor–enzyme complexes (Bora-Tatar et al. 2009). The study revealed that curcumin possesses HDAC inhibition potential with an  $IC_{50}$  of 115  $\mu$ M. Hypoacetylation of histone 3 and 4, at lysine residue, was mediated by curcumin in TREM-1 promotor



**Fig. 1** Curcumin-mediated epigenetic mechanisms involving DNA methylation, histone modifications and microRNA based epigenetic processes

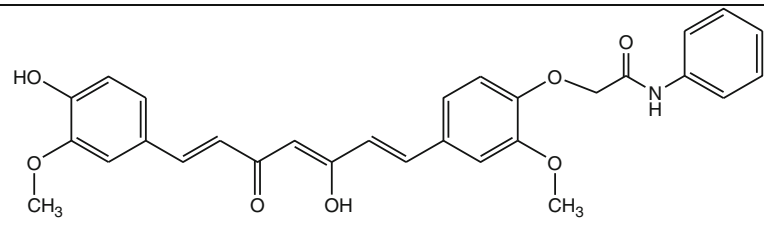
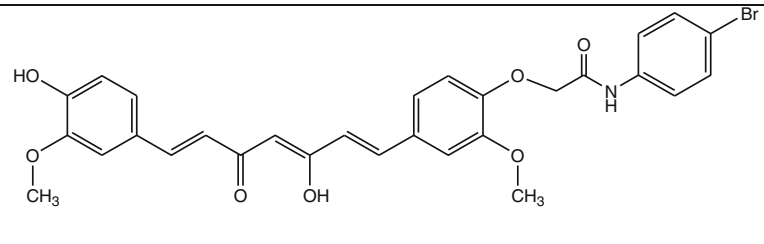
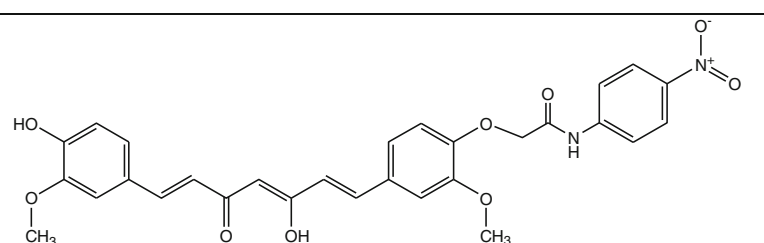
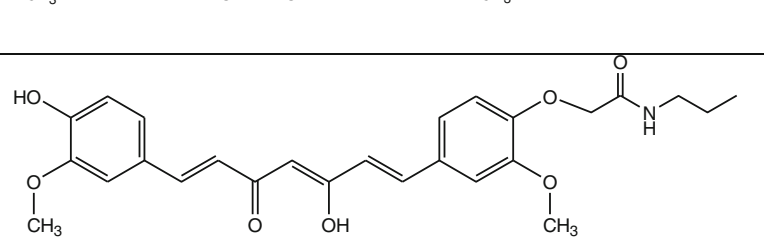
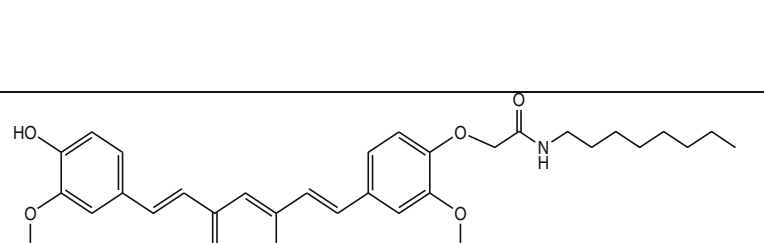


R = H



**Fig. 2** Structure of curcumin (top) and glucuronic acid (bottom). Increase in curcumin solubility and stability with addition of glucuronic acid

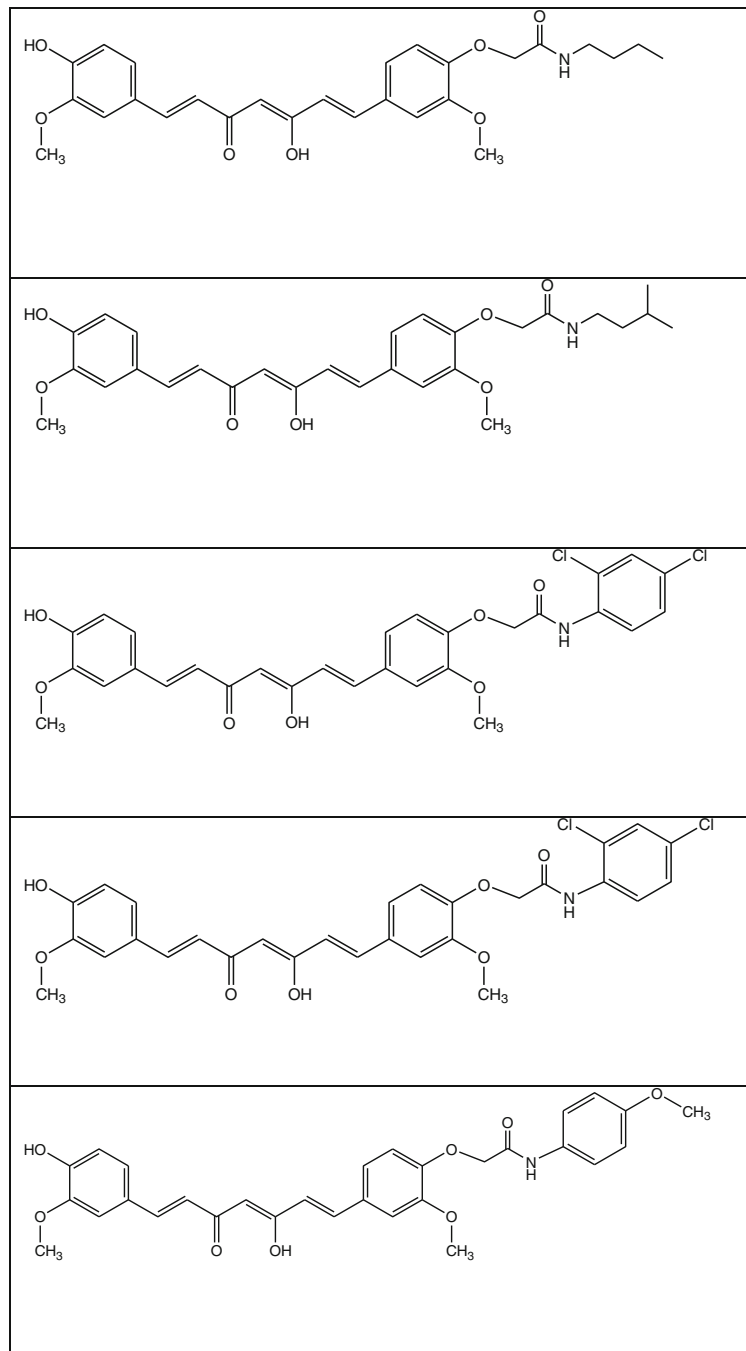
**Table 1** Virtually prepared analogs of curcumin

<b>Virtually prepared analogs of Curcumin</b>	
	
	
	
	
	

region that modulates TREM-1 gene expression (Yuan et al. 2012). Chen et al. reported down-regulation of HDAC-1, HDAC-3, HDAC-8 protein and up-regulation of histone H4 that regulates Raji cell proliferation and apoptosis (Chen et al. 2007). Besides acting on HDAC, curcumin also

inhibits HAT. Zhu et al. (2014b) have determined that curcumin alleviates neuropathic pain by inhibiting p300/CREB-binding protein (CBP) of histone acetyltransferase (HAT) and regulating the expression of BDNF as well as cox-2 in rat. Kang et al. (2006) have shown that

Table 1 (continued)



HAT inhibition by curcumin enhanced Caspase-3-dependent Glioma Cell Death and Neurogenesis of Neural Progenitor Cells. These studies established that curcumin can control acetylation/deacetylation machinery and these processes can alter chromatin structure to control gene expressions. Hence, curcumin being potential HDAC inhibitor can be used to study stroke-induced epigenetic

mechanisms by regulating important machinery (acetylation/deacetylation) in stroke pathogenesis.

#### Curcumin and microRNA

Non-protein coding sequences of DNA that were earlier thought as junk DNA, transcribe non-coding RNAs (nc RNAs).

Micro RNA (miR) is one of the classes of ncRNA that offers tremendous potential in unveiling mechanisms underlying stroke pathogenesis (Qureshi and Mehler 2012). Not only in disease conditions, studies also reflect change in microRNA expression profile in response to therapy (Williams et al. 2009). Mature miRs are derived from stem loop pre-miRNA, possess 20–22 nucleotide length, and regulate gene expression by binding to the 3'-UTR region of their corresponding messenger RNAs (mRNA). Micro RNA along with their target genes are involved in endothelial dysfunction, neuro-vascular integrity, neural differentiation, pro-apoptosis/anti-apoptosis, matrix remodeling, inflammation, angiogenesis and regenerative processes (Barringhaus and Zamore 2009; Chen et al. 2011; Jovanovic and Hengartner 2006; Le et al. 2009; Loyer et al. 2013; Sonkoly and Pivarcsi 2009; Suarez and Sessa 2009; Tan et al. 2011; Wu and Murashov 2013a, b). Although the role of micro RNAs in stroke is still in infancy, the reports indicate their significant contribution in stroke development and unexpectedly stable nature in describing their potential use as diagnostic and prognostic markers (Qureshi and Mehler 2010c; Rink and Khanna 2011). Polymorphism study by Jeon et al. described the association of miR-146a, miR-149, miR-196a2, and miR-499 with cerebral ischemia stroke and silent brain infarction risk (Jeon et al. 2013). Likewise, the study by Zhu et al. (2014a) described the correlation of miR-124 with neuronal death during ischemia/Reperfusion by regulating Ku 70 expression (Zhu et al. 2014a). Khanna et al. described the loss of miR29b with neuronal cell death during stroke (Khanna et al. 2013), and Pandi et al. showed down-regulation of miR-29c in de-repression of DNMT 3a during ischemic brain damage (Pandi et al. 2013). The role of miR140 was studied as a candidate molecule involved in regenerative processes in post-ischemic brain and tissue repair processes after 3 h of middle cerebral artery occlusion (MCAO) (Nicolas et al. 2008). Apart from that, the significant detection of micro RNA in peripheral blood after 24 h of MCAO (mo-miR-19b, mo-miR-290, and mo-miR-292-5p), and 48 h of MCAO (mo-miR-352, mo-miR-26b, mo-miR-26a, mo-miR-20a, mo-miR17, mo-miR-140, mo-miR-92, mo-miR214, mo-miR-15b, and mo-miR-328) suggest their potential as future biomarkers in stroke (Jeyaseelan et al. 2008).

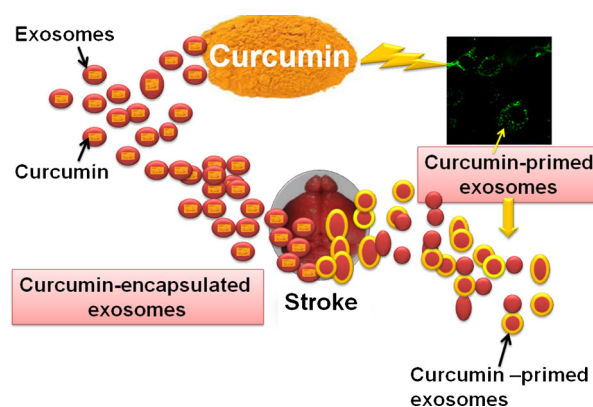
The role of curcumin in regulation of MicroRNA during cerebral stroke has not been studied much. However, curcumin has been studied as neuro-protective agent by regulating Akt/Nrf2, and Nrf2-HO-1 pathways (Wu et al. 2013; Yang et al. 2009). The associations of microRNAs in these mechanisms would further help to elaborate the potential impact of curcumin and its therapeutic efficacy. Moreover, mechanisms induced with therapeutic microRNA, generated with curcumin treatment, can also be studied for different epigenetic processes such as; DNA methylation, histone modification, sumoylation, phosphorylation, and ADP ribosylation.

## Curcumin for stroke prevention

Curcumin possesses multiple pharmacological properties (anti-inflammatory, anti-thrombotic, and anti-oxidative) and these properties further add to its anti-ischemic property. The anti-ischemic effect of curcumin is believed to be contributed by its free radical scavenging activity which is unique due to phenolic and diketonic groups present in its structure. However, other natural anti-oxidants lack the presence of two groups together and possess either of these. The neuroprotective effect of curcumin is well documented over different neurotoxicants; such as Hcy (Kalani et al. 2014a). These protective effects not only rescue the metabolite alterations but also improve brain edema, Evans Blue leakage and infarct size during ischemic brain injury (stroke) (Tyagi et al. 2012). The beneficiary effect of curcumin is also reported to be executed by lowering lipid peroxidation, when administered orally or intraperitoneally (Ghoneim et al. 2002; Thiyagarajan and Sharma 2004). Hence, the major advantages that lay with curcumin treatment have been explored as its non-toxic effect (even at high doses), ability to cross BBB in aged mice and gerbils, and its cerebro-protective behavior (Thiyagarajan and Sharma 2004; Tyagi et al. 2012; Wang et al. 2005).

## Curcumin bioavailability

Although curcumin is demonstrated as efficient and safe in nature, its limited bioavailability continues to be a major concern. Due to its rapid metabolism and elimination, low levels are found in serum and tissue irrespective of the route of administration. Low solubility in water probably reduces its effective action in the target protein site. Different attempts were tried to enhance its bioavailability including; modulation



**Fig. 3** Image showing protective potential of curcumin-encapsulated exosomes (left) and curcumin-primed exosomes (right) during stroke. Curcumin-primed exosomes (labeled with PKH67) are shown as green dots in the image

of the administering route, medium of curcumin administration, structural modifications and encapsulation in exosomes.

### Structural modifications of curcumin

Recently, attempts utilizing structural modifications of curcumin are largely explored to prepare new formulations in order to enhance *in vitro* and *in vivo* efficacies of curcumin. Previously, we have reported protective potential of tetrahydrocurcumin (THC) in amelioration of cerebral ischemia stroke (Tyagi et al. 2012). THC is an active metabolite of curcumin and is more soluble and stable. Therefore, we speculate that curcumin solubility and stability is increased with the insertion of one or two moieties of glucuronic acid at the –OH group which has been presented in Fig. 2. Earlier reports also found increase in solubility of curcumin with similar molecular insertion (Anand et al. 2007). Hence, the addition of glucose to curcumin would enhance its pharmacokinetic properties and candidature as a potential drug molecule.

It has been stated that modification at the –OH group of curcumin has tendency to enhance its activity for Alzheimer's disease (Fang et al. 2014). In the view of recent reports (Fang et al. 2014), some new analogs of curcumin have been virtually designed and the perception has been made that these analogs may find the same or better activity than the parental molecule. Table 1 represents virtually prepared analogs of curcumin; however further QSAR and molecular docking work could confirm their potentials for stroke or stroke-like pathologies.

### Exosomes and curcumin

A recent report by Tiwari et al. (2014) has shown nanoparticle mediated delivery of curcumin to be neuroregenerative which strengthens the therapeutic link towards stroke therapy. Xin et al. describes the potential of exosomes in rat MCAO model (Xin et al. 2013). The investigators derived exosomes from mesenchymal stromal cells (MSC) and used these nano-units against MCAO injury through tail vein injection. They find functional improvements; neurite remodeling, neurogenesis and angiogenesis post MCAO with MSC-exosome treatment which suggests therapeutic efficacy of exosomes. Although exosomes have been implicated in stroke therapeutics, encapsulation of curcumin in exosomes further enhances its protective effects. Investigators have found that curcumin-encapsulated exosomes are highly concentrated in the blood with increased solubility and stability (Sun et al. 2010; Zhuang et al. 2011). Authors confirmed that delivery of curcumin-encapsulated exosomes is beneficial for inflammatory diseases since the approach has no significant side effects (Sun et al. 2010). Interestingly, another report suggests targeted delivery of curcumin-

encapsulated exosomes to the brain through nasal route as a promising, non-invasive and novel therapeutic approach for treating brain inflammatory diseases (Zhuang et al. 2011). We have also observed that curcumin-primed exosomes have potential to recover junction proteins and permeability of endothelial cells (Fig. 3). These novel therapeutic options should be tried in order to alleviate stroke pathology.

### Conclusion and future direction

Although curcumin possess anti-inflammatory, anti-oxidative, neuro-protective, and anti-cancer properties mediated through multiple intercellular/regulatory signaling mechanisms; very little is known about the effect of curcumin on epigenetic aspect during cerebral ischemia stroke. It has been suspected through earlier literature that curcumin possesses epigenetic modulation properties and that's how it affects epigenetic factors, such as HDAC, HAT, DNMTs, and miRNAs. Exploring epigenetic properties of curcumin in neuroprotection potentiates its use in stroke therapeutics. Nonetheless the question that still exists is whether the protective mechanism of curcumin is epigenetically regulated or it has only potential impact? If the epigenetic aspect of curcumin to rescue ischemia stroke becomes clearer, more exciting results can come and give direction for the protective efficacy and therapy. To cope with decreased bioavailability issue, discovery of the novel lead molecules might hopefully bring advancement in the safe and effective treatment of stroke. However, further, QSAR and docking guided lead optimization is under progress, which will assist in elucidating the precise mechanism of action. Alongside, exciting results on the use of curcumin-encapsulated/curcumin-derived exosomes pave the way to the future novel therapeutics in cerebral stroke where drug target is still a challenge.

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**Conflict of interest** The authors declared no conflict of interest.

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