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Review

Curcumin and hormesis with particular emphasis on neural cells

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ABSTRACT

Curcumin is shown to commonly induce biphasic dose responses in a broad range of cell types, with particular emphasis on neural cells, including neuronal stem cells. The quantitative features of these biphasic dose responses, with respect to the magnitude and width of the low dose stimulation, are similar to those reported for hormetic dose responses. These hormetic dose responses occur within the framework of direct stimulatory responses as well as in preconditioning experimental protocols, displaying acquired resistance within an adaptive homeodynamic framework. These findings have important implications for study design strategies involving dose selection and spacing, as well as sample size and statistical power considerations. These findings further reflect the broadly general occurrence of hormetic dose responses that consistently appear to be independent of biological model, endpoint, inducing agent and mechanism.

1. Introduction

Curcumin is the principal component of turmeric that has long been widely used in Indian dietary practices. It has also been used in many countries as a means to treat a spectrum of inflammatory diseases. A vast literature exists showing that curcumin exhibits a complex array of pharmacological effects that include antioxidant, anti-inflammatory, and anti-tumor effects (Prasad et al., 2014). Curcumin can protect brain cells in a broad range of neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, and stroke (Cole et al., 2007; Lee et al., 2014). Despite the substantial literature on the biomedical effects of curcumin, its limited bioavailability, poor water solubility, and rapid metabolism/excretion have limited its use as an effective therapeutic, including applications for neurodegenerative diseases (Maiti and Dunbar, 2018). While much effort has been made to develop commercial products that enhance curcumin bioavailability, curcumin dose response curves are often biphasic (Cole et al., 2007; Moghaddam et al., 2018), a factor that may have significant public health and therapeutic implications within various bioavailability/pharmacokinetic contexts. The present paper provides an evaluation of the occurrence of curcumin induced biphasic dose responses on neuronal stem cells, non-stem neural cells, and other cell types, including non-neuronal stem cells. The findings suggest that hormetic-like biphasic dose responses are a common feature of curcumin induced biological effects with important implications for study designs, including the number and the spacing of doses as well as for possible therapeutic applications and public health practices.

2. Search strategy

PubMed, Web of Science, and Google Scholar data bases were searched for articles using the terms “hormesis or hormetic and curcumin; biphasic dose response and curcumin; U-shaped and curcumin; U-shaped dose response and curcumin; preconditioning and curcumin; adaptive response and curcumin; stem cells and curcumin; curcumin and dose response; curcumin and concentration response; curcumin and conditioning response.” All relevant articles were evaluated for the references cited and for all papers citing these papers. All research groups publishing on curcumin dose response relations were assessed for possible relevant publications in the above data bases.

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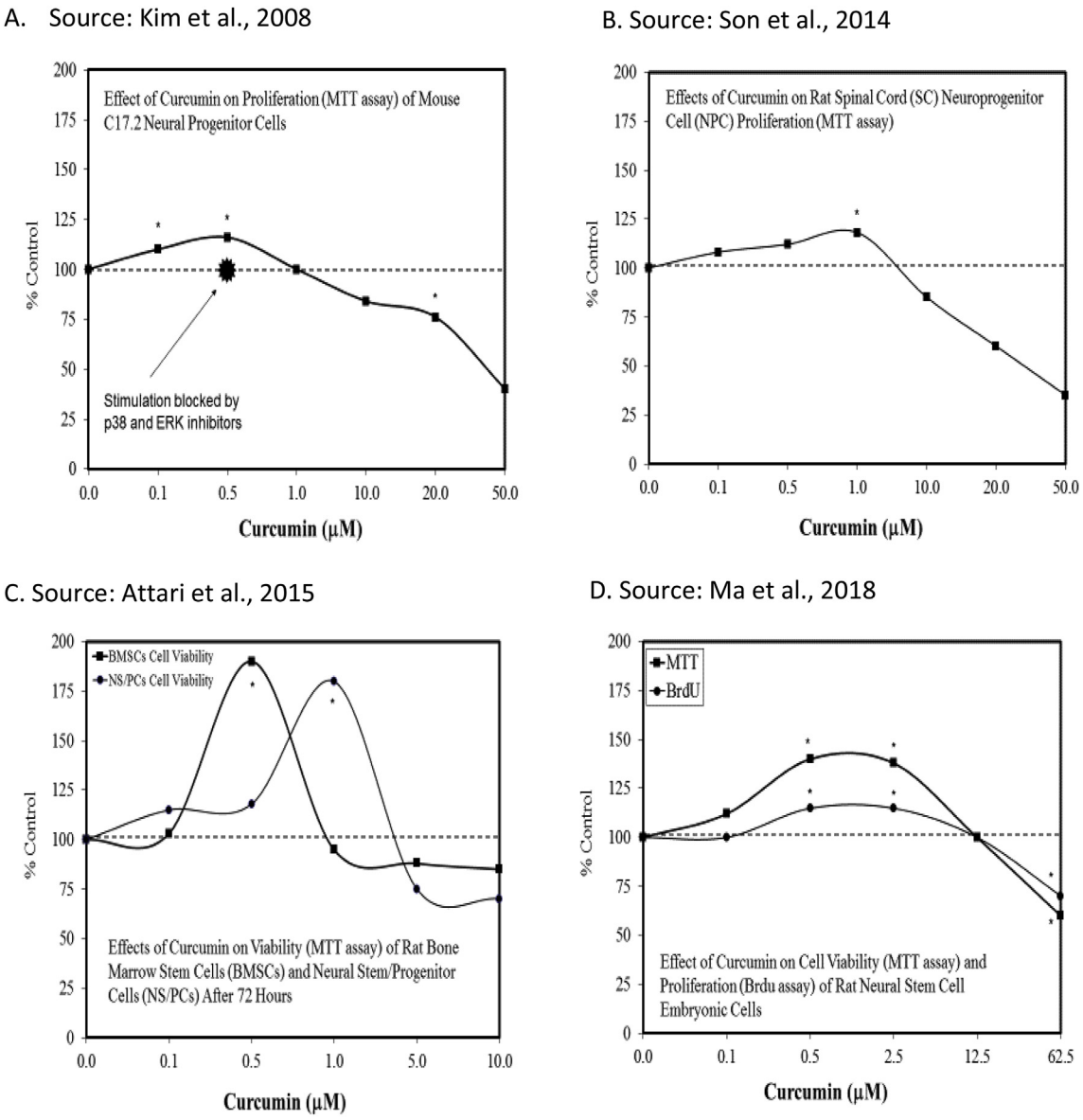


Fig. 1. Effects of curcumin on neural stem cells.

3. Curcumin induced hormetic effect

3.1. Neural stem cells

Four experimental papers on the hormetic effects of curcumin on neuronal stem cells have been published. These papers originated from four different research groups, two from South Korea (Kim et al., 2008-Fig. 1A; Son et al., 2014-Fig. 1B) one from Iran (Attari et al., 2015-Fig. 1C) and the other from China (Ma et al., 2018-Fig. 1D). Each study used a different type of neuronal stem cell. Several groups used Sprague-Dawley rats, with Ma et al. (2018) using cells derived from the day 15 embryonic cortex, while Son et al. (2014) obtained stem cells from chopped up spinal cord of 250–350 g adult animals. In the case of Attari et al. (2015) they used stem cells derived from the SVZ brain region from young adult (150–200 g) Wistar rats. Kim et al. (2008) was the only group to employ a mouse model, using C17.2 cells originally derived from the cerebellum of a four-day old neonatal mouse. Thus, the four papers offered differing models with different developmental periods and locations for the source of the neuronal stem cells. While three of the papers (Kim et al., 2008; Son et al., 2014; Ma et al., 2018) addressed possible cell signaling pathways of curcumin, Attari et al. (2015) clarified the optimal dose and treatment period (i.e., duration of exposure) to affect a maximum response. The four studies measured cell proliferation with the same MTT/MTS endpoint with Ma et al. (2018) (Fig. 1D) and Kim et al. (2008) (Fig. 1A) measuring the response at 24 h, Son et al. (2014) (Fig. 1B) at 48 h and Attari at 48 and 72 h (Fig. 1C). All used similar microplate reader methods with the same temperature and four-hour incubation period [except for Son et al. (2014) 2.5 h] but with somewhat differing absorbance values used: 560 nm (Kim et al., 2008; Ma et al., 2018), 595 nm (Attari et al., 2015), 490 nm (Son et al., 2014). The number of concentrations tested was five or six, which covered a concentration range of 100 (Attari et al., 2015) to 500 (Kim et al., 2008; Son et al., 2014) to 625-fold (Ma et al., 2018). While most seeded 1×10^4 cells per well, Ma et al. (2018) seeded five times as many cells (5×10^4).

As seen in Fig. 1 a hormetic-like biphasic dose response was reported for each study. There was inter-study variation with respect to the maximum stimulation and the range of stimulation. The maximum response ranged from a low 116 to a high of 190%. The width of the stimulatory response ranged from a low of < five-fold (not precisely defined) to approximately 25-fold. Of potential significance is that Attari et al. (2015) reported no treatment effects at 48 h but a marked

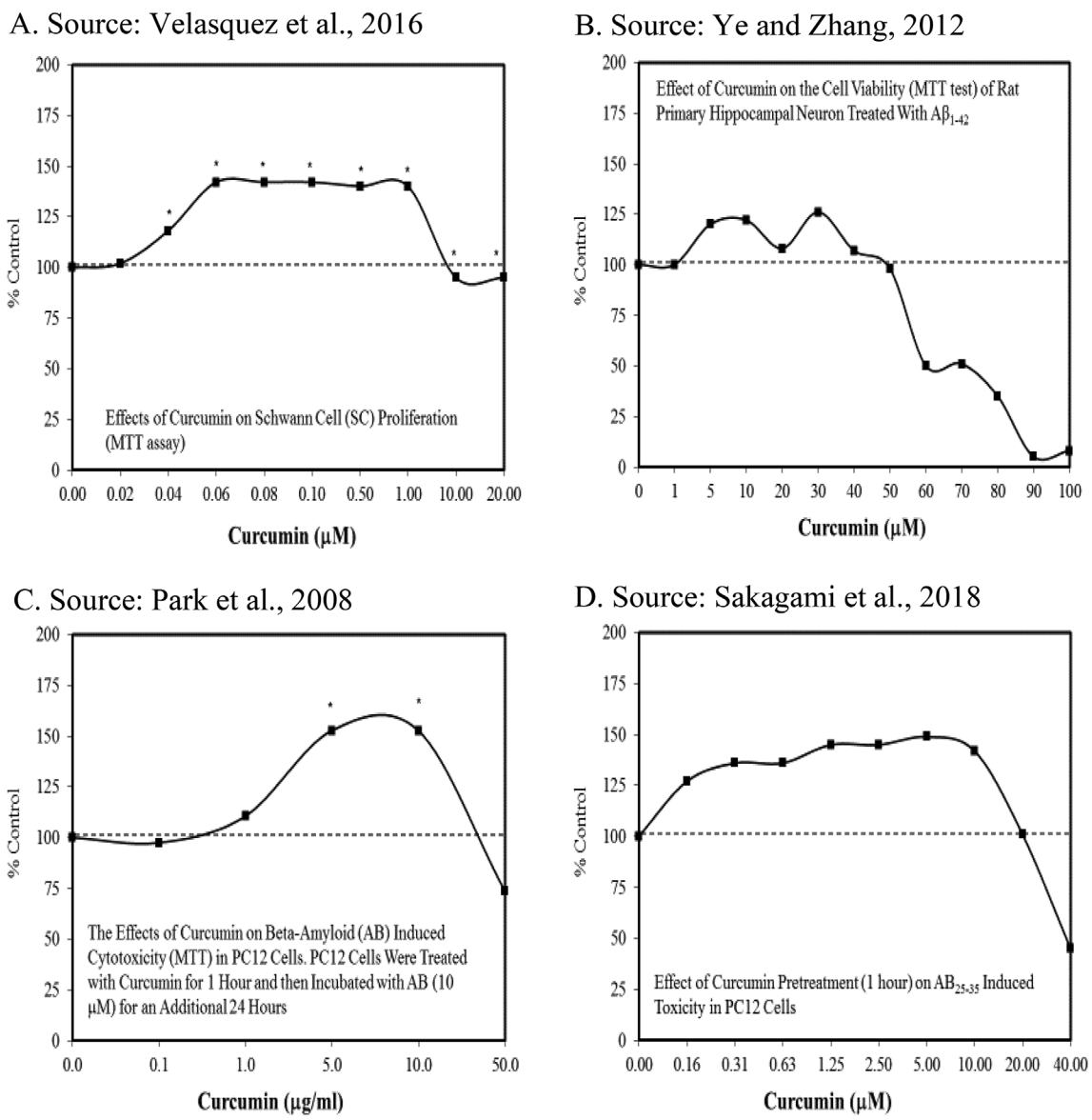


Fig. 2. Effects of curcumin on non-stem neural cells.

hormesis stimulation at 72 h. No other neuronal stem cell papers evaluated here measured the response at more than one time-period.

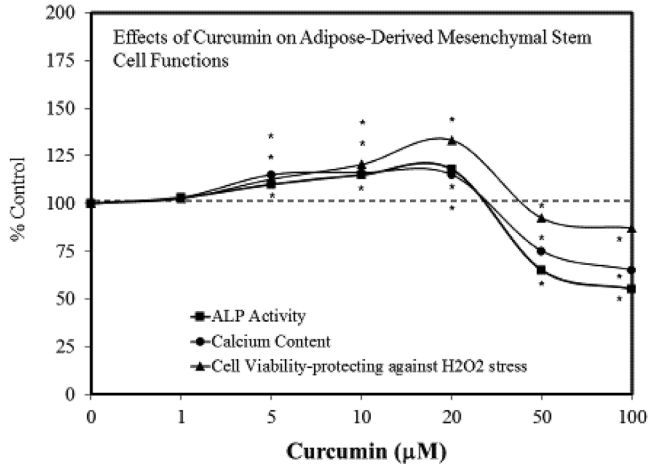
Both Kim et al. (2008) and Son et al. (2014) reported that curcumin activated the p38 MAP kinase and MEK/ERK pathways. Blockage of these pathways with specific inhibitors abolished the increase in proliferation due to curcumin, thereby providing evidence of pathway mediation. Similar experiments provided no evidence for JNK pathway involvement in the curcumin-induced cell proliferation stimulation. In a complementary analysis, Ma et al. (2018) demonstrated that a low dose curcumin-treatment enhanced cell proliferation was also dependent upon the glucocorticoid receptor and STAT3 in the rat embryonic neural stem cell model.

3.2. Generality of Curcumin's capacity to induce hormesis

3.2.1. Non-stem neural cell responses

While the capacity of curcumin to affect neural stem cells via hormetic mechanisms has been studied only to a limited extent, the findings evaluated here are consistent across several different rodent models as well as range of neuronal stem cells. The quantitative features of the hormetic biphasic dose responses are consistent with those reported in the published hormesis literature (Calabrese and Blain, 2005, 2009, 2011; Calabrese and Mattson, 2017; Calabrese et al., 2019). Furthermore, these results are consistent with an expanded spectrum of findings with curcumin that displayed hormetic effects with other neuronal biological model systems. These include a diverse set of non-stem nerve cell responses: the effects of curcumin on cell proliferation in PC12 cells (Liao et al., 2012), and Schwann cells (Velasquez et al., 2016) (Fig. 2A), protection in Huntington's disease models (Hickey et al., 2012; Chongtham and Agrawal, 2016) and protection of neurons against beta amyloid (Fig. 2B–D) (Park et al., 2008; Sakagami et al., 2018; Ye and Zhang, 2012; Maiti and Dunbar, 2017; Yagi et al., 2013), protection from amyloid pathology in the Alzheimer's transgenic mouse model (Lim et al., 2001) and enhancing viability of primary cultures of the rat striatum (Nazari et al., 2013), preventing rotenone and salsolinol (Qualls et al., 2014) induced oxidative stress/cell damage, and preventing Cu^{2+} induced oxidative stress in primary rat cortical neurons (Huang et al., 2011). In several cases, there were 9–12 concentrations employed (Velasquez et al., 2016; Ye and Zhang, 2012; Sakagami et al., 2018), enhancing the capacity to offer descriptive insight on the quantitative features of these hormetic-biphasic dose responses.

A. Source: Wang et al., 2016



B. Source: Kim et al., 2011

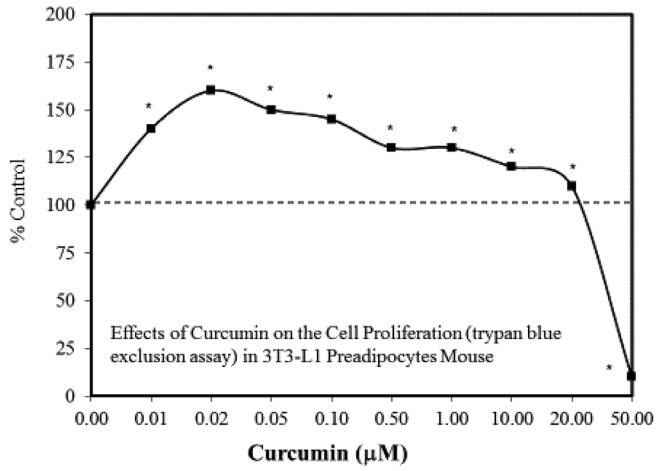


Fig. 3. Effects of curcumin on non-neuronal stem cell responses.

3.2.2. Non-neuronal stem cell responses

Further generalizing the capacity of curcumin to mediate biological responses via the hormetic dose response was its ability to act in a similar fashion in other types of stem cells such as human mesenchymal stem cells (Wang et al., 2016) (Fig. 3A) while enhancing resilience against H_2O_2-induced oxidative stress, and cell proliferation at low doses. The curcumin derivative Bis[2-hydroxybenzylidene]acetone (BHBA) also enhanced resilience in a hormetic fashion, protecting against As(III)-induced cytotoxicity (Shen et al., 2015). Likewise, curcumin enhanced the cell proliferation of mouse 3T3-L1 preadipocytes in a hormetic manner (Kim et al., 2011) (Fig. 3B). In this experiment, the stimulatory range was at least 1000-fold. The stimulatory concentration range was probably larger since at the lowest concentration tested cell proliferation was still significantly greater than control values.

In an extensive assessment of proliferation-related proteins and transcription factors, Kim et al. (2011) found that curcumin markedly activated phosphoinositide 3-kinase (PI3K) and its downstream mediators, phosphorylated-mitogen activated protein kinases (MAPK)/extracellular signal-regulated protein kinase (ERK) (p-MEK), pERK and pAKT of 3T3-L1 preadipocytes. However, it decreased apoptosis-related proteins, p38 MAPK and JNK. Thus, curcumin enhances 3T3-L1 cell proliferation through activation of PI3K and MEK signaling pathways while inhibiting p38 and pSAPK/JNK. The direct inhibition of p38 contrasts with the mechanistic pattern in neuronal stem cells. Curcumin also induced the overexpression of c-Myc protein and the down-regulation of the tumor suppressor, p53 (Kim et al., 2011).

3.2.3. Other hormetic responses

The capacity of curcumin to affect other biological systems in a hormetic manner has also been shown for human keratinocyte proteasome activity (Ali and Rattan, 2006) (Fig. 4A), human skin fibroblast wound healing (Demirovic and Rattan, 2011) (Fig. 4B), reducing inflammation in buffalo granulosa cells (Vashisht et al., 2018) (Fig. 4C), the proliferation of olfactory ensheating cells in transgenic mice (Velasquez et al., 2014), erythrocyte Na^+/K^+-ATPase activity (Singh et al., 2015) (Fig. 4D), heme oxygenase-1 activity in astrocytes (Scapagnini et al., 2002), vascular endothelial cells (Motterlini et al., 2000), Hut-78 cells (Anto et al., 2002), ubiquitin activating enzyme E1-like (UBE1L) in human bronchial epithelial cells (Beas-2β cells) (Jiang et al., 2015), as well as cell proliferation in multiple tumor cell lines (Fig. 4E–H) (Santel et al., 2008; Collins et al., 2013; Deng et al., 2018; Zhou et al., 2014; Shen et al., 2015). Curcumin also mediated cell death, enhancing apoptosis at low and necrosis at higher doses in a human osteoblast cell line (Chan et al., 2006) affecting an ATP switching mechanism. In the case of renal cell carcinomas the low dose stimulation was mediated via the AMPK and ER stress pathways while the high dose inhibitory/toxicity effects were mediated at least in part by the oxidative stress pathway (Deng et al., 2018). These findings demonstrate that curcumin can activate autophagy via the AMPK, and ER stress pathways and oxidative stress pathways. This links autophagy with both the enhancement of survival at low doses and with cell death at higher doses. Evaluation of the effects of curcumin on autophagy protein markers for AMPK and ER pathways also revealed hormetic dose responses (Deng et al., 2018). Finally, while the above studies of curcumin-induced hormetic responses were *in vitro* cell studies, Tanwar et al. (2010) reported curcumin induced hormetic response in male Wistar rat *in vivo*. At low doses the curcumin upregulated endogenous antioxidant systems whereas at higher doses it led to enhanced ROS formation, suppressing GSH and SOD formation The low dose of curcumin also protected against isoprenaline induced cardiac damage while exacerbating it at higher doses based on multiple endpoints.

4. Discussion

These collective findings indicate that curcumin displays a general capacity to induce hormetic dose response relationships within a range of neural and other types of stem cells, as well as other non-stem cell activities, including several chemoprotection models against beta amyloid. The studies supporting this conclusion have particularly strong study designs based on the number of concentrations employed, generally being in the six to twelve concentration number range. The use of large numbers of concentrations provides the capacity to explore a broad dose response continuum including both low dose stimulatory and the high dose inhibitory and/or toxicity domains. Despite the limited number and range of curcumin-induced hormetic responses, the findings suggest that the capacity of curcumin to induce low dose stimulatory responses is often in the 30–60% range above the control, that is, in the hormetic stimulatory zone, as generally shown in this paper (Calabrese and Blain, 2005, 2011).

The present evidence establishes curcumin as a widely acting hormetic agent that activates adaptive cellular stress response pathways as has been demonstrated for other dietary phytochemicals (Mattson, 2015). Recognition of this capacity to induce hormetic responses may be useful to investigators as it may affect study design, dose number selection and spacing, and statistical power considerations. Additional findings on mechanisms suggest elements of a common pathway strategy in several nerve cell models (Kim et al., 2008; Lee et al., 2014; Son et al., 2014), 3T3-L1 preadipocyte stem cells (Kim et al., 2011) and for autophagy pathways mediating hormetic effects in several renal tumor cell lines (Deng et al., 2018).

The curcumin concentrations over which hormetic stimulation were reported range over a broad spectrum of cell types. While the available data are not extensive, it may be possible to discern some suggested

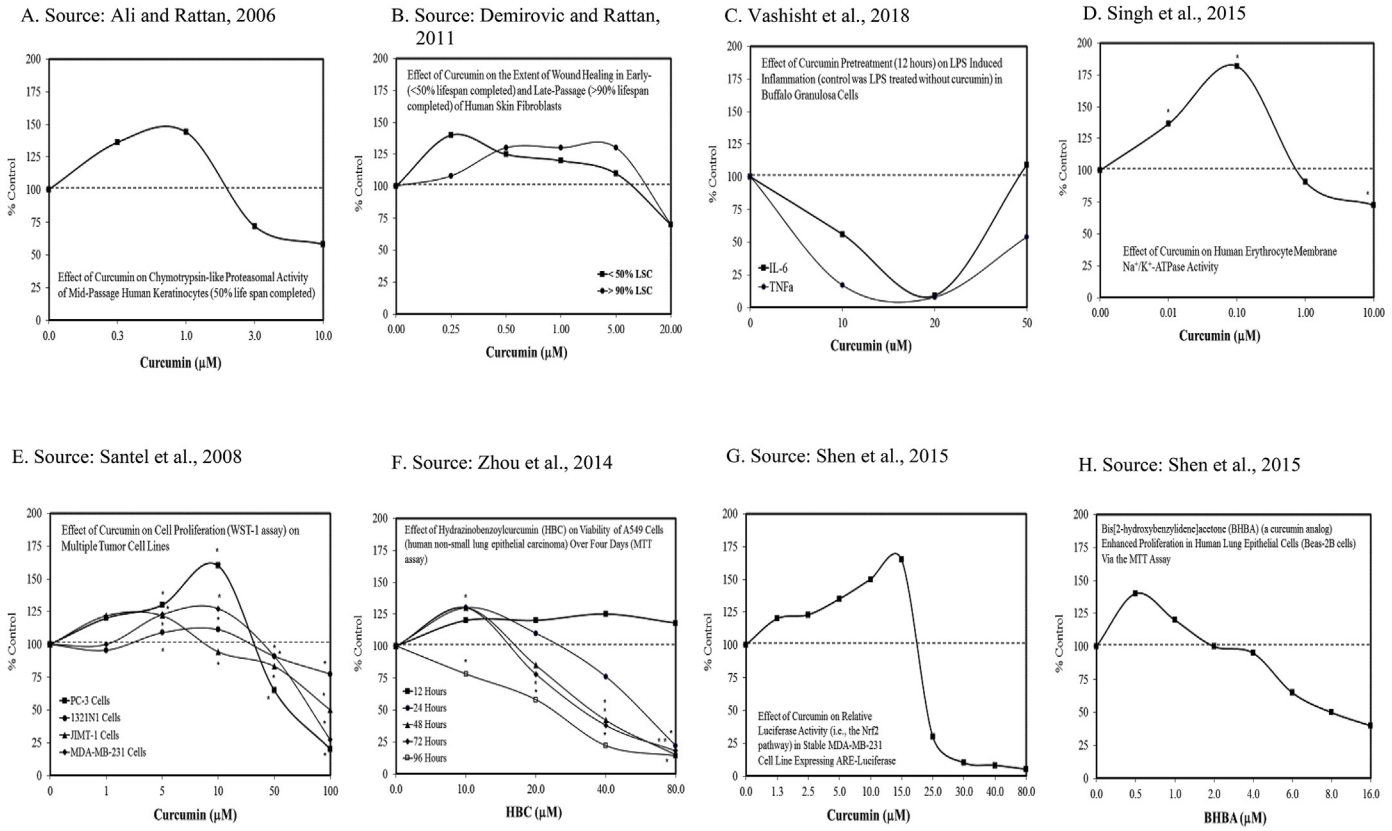


Fig. 4. Effect of curcumin on diverse cell types and functions.

response patterns that need to be assessed further. For example, the neuronal stem and non-stem cells tend to display maximum stimulatory responses in the 0.1–1.0 μM range, whereas in tumor cells maximum stimulation occurs over a higher concentration range (1–10 μM), about 10-fold. A further observation was that neuronal cells challenged with $A\beta_{1\text{-}42}$ (Park et al., 2008; Ye and Zhang, 2012; Yagi et al., 2013) tend to show optimal curcumin induced protection at concentrations of 10–20 μM. Whether such hormetic stimulatory patterns can be confirmed and generalized remain a research question with considerable public health and medical implications.

Of potential practical significance is that concentrations used in several studies showing hormetic effects were within (and at times lower) the concentration range seen in human blood monitoring studies (Liao et al., 2012). This suggests the possibility that an optimal dosing scheme could be developed for public health and therapeutic applications. This possibility may be further supported since advances have been made in the development of commercially available bioavailable curcumin products (Rakotoarisoa and Angelova, 2018; Maiti and Dunbar, 2018; Hewlings and Kalman, 2017). The fine-tuning and optimizing of exposure protocols to achieve biological/public health endpoint goals is of strong interest. While the predominant interest in the consumption of curcumin relates to its potential health benefits, several studies showing that curcumin can enhance the *in vitro* proliferation of some tumor cells, including decreasing the tumor suppressor p53 (Kim et al., 2011), raise important research questions, especially in light of rapid changes in commercial products that markedly increase the bioavailability of curcumin.

5. Conclusion

Curcumin commonly displays hormetic dose responses. These findings show a capacity for broad generalization, suggesting that the hormetic responses for curcumin may be independent of biological model, cell type, and endpoint. The present findings have important implications for study design, including selection of doses and sample size. The findings may also have implications for humans who ingest substantial quantities of curcumin with and without consideration of bioavailability related to optimal dosing.

Conflict of interests

All authors declare no conflict of interest.

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