Hormetic approaches to the treatment of Parkinson's disease: Perspectives and possibilities

HORMETIC APPROACHES TO THE TREATMENT OF PARKINSON'S DISEASE: PERSPECTIVES AND POSSIBILITIES

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ABSTRACT

Age-related changes in the brain reflect a dynamic interaction of genetic, epigenetic, phenotypic and environmental factors that can be temporally restricted or more longitudinally present throughout the lifespan. Fundamental to these mechanisms is the capacity for physiological adaptation through modulation of diverse molecular and biochemical signaling occurring from the intracellular to the network-systemic level throughout the brain. A number of agents that affect the onset and progression of Parkinson's disease (PD)-like effects in experimental models exhibit temporal features, and mechanisms of hormetic dose responses. These findings have particular significance since the hormetic dose response describes the amplitude and range of potential therapeutic effects, thereby affecting the design and conduct of studies of interventions against PD (and other neurodegenerative diseases), and may also be important to a broader consideration of hormetic processes in resilient adaptive responses that might afford protection against the onset and/or progression of PD and related disorders.

Significance Statement

This paper provides the first integrative assessment concerning how the concept of hormesis may play a significant role in preventing the onset and severity of Parkinson's disease symptoms and disease processes. This paper identified and assessed 50 different potential chemotherapeutic agents that act via hormetic mechanisms and within the context of the quantitative features of the hormetic response to prevent Parkinson's disease related effects. The use of hormetic strategies should become a central component in the prevention of chronic neurodegenerative diseases such as Parkinson's.

INTRODUCTION: ADDRESSING THE PREVALENCE OF AGE-RELATED NEURODEGENERATIVE DISORDERS

A major complication of normal healthy aging is an incremental risk of age-related conditions that can increase morbidity and adversely affect the quality of life. Indeed, with a lengthening life span of the global population, there is concomitant rise in the prevalence of neurodegenerative disorders such as Parkinson's (PD) and Alzheimer's (AD) disease (Kim et al., 2016; Li and Le,2013). Thus, persistent – and important – questions, and ongoing research focus both upon those factors that may contribute to the development and progression of these disorders, and if, how and to what extent these patho-etiologic variables might be mitigated and/or prevented..

Age-related changes in the brain reflect a dynamic interaction of genetic, epigenetic, phenotypic and environmental factors that can be temporally restricted or more longitudinally present throughout the lifespan. Fundamental to these mechanisms is the capacity for physiological adaptation through modulation of diverse molecular and biochemical signaling occurring from the intracellular to the network-systemic level throughout the brain. In this context, hormesis defines thresholds of adaptive responses that have been shown to evoke and sustain adaptive plasticity to a range of stimuli and conditions (Calabrese. et al., 2010; Calabrese et al., 2015).

HORMESIS: BACKGROUND AND PERSPECTIVES

A number of stressor agents can induce adaptive responses at low doses, but are less effective, and in some cases are even toxic at increasingly higher doses. This biphasic dose response pattern (i.e.- low dose stimulation and high dose inhibition) is called hormesis, from the Greek, meaning "to excite" (Calabrese EJ and Baldwin, 2002; Mattson, 2008). The concept of hormesis was first reported by Schulz (1887, 1888) who noted that low doses of many disinfecting agents enhanced yeast metabolism and survival at low doses, but became toxic at increasing doses. Other investigators extended these initial observations to reveal that biphasic dose responses are a highly generalized occurrence in and across all phyla and in numerous cell types. Calabrese and Baldwin (2000a, b) have summarized the historical development of the concept of

hormesis and its properties and putative mechanisms in response to a variety of chemical and ionizing radiation stimuli (Calabrese and Baldwin, 2000a,b). Yet, despite substantial documentation of hormetic dose responses in the scientific literature (Calabrese and Blain 2005,2011), fields such as toxicology have long employed high doses to characterize biological responses, with extrapolation to low doses via linear and/threshold dose-response models. However, over the past several decades, there have been expanded investigations of biological responses to low doses of chemicals and radiation that have often revealed hormetic dose-response relationships, and more recently demonstrated the mechanistic bases of their effect(s) (Calabrese, 2013a).

These studies have shown hormetic dose responses to typically elicit a modest stimulatory effect, which is usually in the maximum range of 30-60% greater than control. Such stimulatory responses reflect either a direct stimulation or an over-compensatory effect, and occur independently of biological model, cell type, inducing agent, and mechanism (Calabrese 2011, 2013a). Hormetic effects are currently being ever more considered for biomedically therapeutic applications (Calabrese EJ, 2008a) in that these responses appear to be involved in a number of developmental, maturational and aging processes (Segev-Amzaleg , 2013; Calabrese et al., 2015), and may subserve a spectrum of activities in neural systems, including protection against and/or recovery from certain neurodegenerative diseases, and/or injury (Calabrese EJ, 2008b; Calabrese 2013b). The iterative recognition of hormesis has occurred in large part because traditional dose-response constructs, such as the threshold model, have not been able to satisfactorily and/or fully account for non-random biological activity below well-established thresholds of response.

HORMESIS AND PARKINSON'S DISEASE

Consideration of employing hormetic models and approaches for therapeutics against neurodegenerative disorders is relatively recent, and has emerged only over the past 15 years (Calabrese, 2008c-e; Calabrese et al., 2017). For example, research linking hormetic mechanisms to Parkinson's disease (PD) has focused upon the ways that potential therapeutic agents may act within an experimental pre-conditioning framework to modify adaptive mechanisms that prevent

or diminish effects induced by 6-hydroxydopamine (6-OHDA) and/or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).

Interest in expanding this research to clinical translational applications is based upon concerns that long term treatment of PD with levodopa often leads to end-of-dose and/or tachyphylactic exacerbation of signs and symptoms, and can evoke significant side effects, such as dyskinesia (Shulman et al.,2001). These deleterious effects have prompted the search for agents that might be useful in the prevention and treatment of PD, inclusive of other pharmacological approaches (Carradori et al., 2015; Huleatt et al., 2015), the use of low dose radiation (Kojima et al.,1999; El-Ghazaly et al.,2015) and herbal extracts, many of which are constituents of traditional Asian pharmacopeia (Zhang et al.,2015). Several candidate agents have been screened using *in vitro* models (e.g. - PC-12, SH-SY5Y and MN9 cells) that mimic key features of PD when exposed to agents such as 6-OHDA, MPTP, rotenone and paraquat. Agents eliciting positive effect(s) in these *in vitro* models may be selected for further evaluation using *in vivo* rodent models. But it is of particular interest that *in vitro* testing of possible therapeutic agents for PD often involves a broad range of concentrations, permitting an enhanced assessment of the dose/concentration-response relationship. Within this framework, a number of studies have identified possible therapeutic agents for PD. Many of the agents tested show therapeutic potential to diminish PD-like effects. Yet, it is common for such studies to evaluate only a modest range of concentrations, and thus limit the opportunity to assess a broader dose-response pattern. It is also of note that most of the papers published only evaluated the potential for reducing PD-like effects using a pre-conditioning protocol, with little attempt to apply the potential therapeutic agent within post-conditioning protocols (that may have clinical relevance).

Despite such constraints and limitations, it is noteworthy that a significant number of studies have evaluated potential PD treatments within a broad dose response framework. As summarized in Table 1, this literature has identified approximately 50 agents that display capacity to prevent some PD related effects in one or more experimental models. Of these agents, the majority are of plant

origin, with the remaining being either endogenous (e.g. creatine, estrogen, orexin, OEA) or synthetic substances (lactocystin, apomorphine, and glucose oxidase). One agent (OEA) was both of plant origin and endogenous in mammalian systems. Several of the herbal agents were complex mixtures, such as Hepad, which is comprised of six different herbal substances. Another therapeutic treatment, YGS, a treatment used in traditional Chinese medicine, is a mixture of nine different herbal extracts. These studies were published from 1996 to 2017, with the majority since 2007.

Table 1 about here

Experimental Models of Parkinson's Disease: Inducing Agents and Dose-Response Features

A number of agents have been tested in at least one of 11 PD experimental testing systems, and involved the use of 3 *in vitro* cell lines (PC-12, SH-SY5Y and MN9), or *ex vivo* mouse or rat substantia nigra and/or hippocampal cells. The agents most commonly employed to induce cellular effects were 6-OHDA, MPTP/MPP+, salsolinol, hydrogen peroxide (H2O2), L-dopa and glutamate. Of particular significance to assessing possible hormetic effects was the selection/number of doses, and the dose range(s) in which the agents were evaluated. Typically, 3-10 treatment doses were used, and dose ranges varied between 3-fold (Xiao-Qing et al.,2005) to 100,000-fold (Ba et al., 2004), with the majority of experiments employing a dose range of $\leq$100 fold (see Tables 2 and 3). The timing of the chemoprotective treatments prior to the administration of the PD-inducing agent (e.g., 6-OHDA, MPTP) was also highly variable, ranging from a low of 15 minutes (i.e., apomorphine; Gassen et al., 1998a; polyphenols; Levites et al., 2002) to a high of 14 days (i.e., nicotine; Ryan et al., 2001; creatine; Matthews et al., 1999), with prior treatment exposures of 1 and 24 hours being most characteristically utilized.

Evaluation of the compounds/mixtures tested revealed substantial reduction in damages induced by (the subsequent) toxic agent(s). At the optimum dose, the reduction in pathogenic effects was approximately 30-60%, with some treatments approaching complete protection. The protective dose range varied according to the biological model, agent, endpoint, toxic threshold response concentration, and study design used (see Tables 1 and 2)[1]. The quantitative features of the hormetic dose response in these PD experiments

are fully consistent with those described in the hormesis literature. The most striking similarity of the quantitative features of hormetic dose responses is the modest increase in amplitude, which occurs whether the response is a direct stimulation, as an over-compensation to a disruption in homeostasis, or within pre- and post-conditioning frameworks. Such quantitative consistency suggests that the amplitude of the hormetic dose-response provides a (quantitative) indicant of the limits of biological plasticity (Calabrese, 2013c; Calabrese and Mattson, 2011). In contrast to the striking consistency in amplitude is the more variable width of the protective response. While there is considerable research describing mechanisms of the biphasic hormetic dose- response, these studies have not provided insight to factors that affect the magnitude or width of the stimulatory response. Thus, there is little understanding of how the amplitude of the hormetic response may be "regulated", or how it could be experimentally manipulated.

Tables 2 and 3 about here

Assessment of other agents that evidenced protection against pathogenic effects in standard PD experimental models (but with typically more limited dose-range features) also showed a consistently similar maximum therapeutic effect in the 30-60% range (Levites et al.,2002; Nie et al., 2002; Soliman et al., 2016). However, these experiments typically did not include a (broader) dose range that permitted more thorough evaluation of effects incurred at low(er) or high(er) doses (e.g. - regressing toward the control group at lower doses, or becoming toxic and enhancing PD-like effects at higher concentrations)

The studies included in this report were chosen because they permitted assessment of an extended dose-response range, and their dose-response features were fully consistent with those observed when using *a priori* evaluative criteria (Calabrese EJ and Blain 2005, 2011; Calabrese EJ and Baldwin 2001, 2003). Thus, the features seen in these PD studies conform to hormetic dose-response patterns. These observations have important clinical implications in that they suggest the potential benefit that such agents (theoretically) might afford. The induced protective responses

seen in the PD models used are similar to those reported when pre-conditioning is employed in other biological systems, for other endpoints, and when using other inducing agents (Calabrese EJ,2016a,b). Therefore, we posit that the quantitative dose-response features of the these protective effects may be regarded as relatively generalizable.

An experimental approach to assess agents' capacity to prevent and/or slow the progression of PD-like effects involves the pretreatment of a model biological system (such as PC12 or SH-SY5Y cells) with the agents of interest. Pretreated cells are subsequently perfused with 6-OHDA, rotenone, paraquat or other substances that induce a cellular stress and/or toxic response. In the majority of these experiments, by the end of the study, the control value (i.e., group treated only with the stressing agent) of cellular function decreased to about 40-60% of that of the original control (unexposed controls). The current literature does not provide information on the temporal changes in control values (i.e.- after treatment with the stressing/toxic agent) until the end of the study. Hence, there is no information on the extent of recovery in the control group during the experimental period, nor is there information detailing the rate of injury/damage induced.

This experimental situation is complex, as the control group displays considerable induced damage that is presumed to be followed by recovery. However, cells pretreated with therapeutic agents may not be directly comparable to the control cells, as it is not possible to know whether reduction in damage is due to less insult induced, a greater capacity for repair/recovery, or some combination of both. This issue may be clinically relevant given that preventing damage would be an important consideration (and approach) for interventions in individuals who may be predisposed to PD. On the other hand, mitigating and/or prompting recovery from pathologic changes and effects would be important in the treatment of those who have already developed the disease.

Most published findings on hormetic responses for PD treatments employ time points, pairing of pretreatment and stressing agents, and delivery methods that render their protocols difficult for translational application (or perhaps even direct extrapolation) to clinical scenarios relevant to the prevention or therapeutics of PD (and other neurodegenerative disorders). Despite

this, the fact that hormetic responses occur, and have been shown to exert neuroprotective and recuperative effects in *in vitro*, *ex vivo* and *in vivo* models both compels the need for further and more detailed research, and maintains potential utility of hormetic approaches in therapeutic settings.

Putative Mechanisms

Any such research should also strive to elucidate and/or build upon prior studies of mechanism(s) of action and effect. Many of the studies cited in the present paper demonstrating hormetic effects elucidate specific receptor- and/or organellar-based pathways. And while these papers reveal a broad range of mechanisms depending on the biological model and cell type, none defined mechanisms that may be operative in *both* stimulation and inhibition responses. For example, the same receptor may mediate a stimulatory *or* inhibitory effect; or may subserve stimulation *and* inhibition responses. As well, responses may involve activation of several intracellular (i.e. - receptor-linked and non-receptor-linked) pathways (Lo et al., 2008). Figure 1 presents an overview of those receptors and pathways that have been shown to mediate hormetic stimulatory responses for 15 sample agents. Of particular interest is the similarity of quantitative features of the dose response, regardless of cell type or mechanism.

Figure 1 about here

While it is understandable that investigators may tend to focus attention on the stimulatory/adaptive aspects of the dose-response in these neural models, an enhanced understanding of mechanisms mediating the stimulatory *as well as* inhibitory components of the hormetic dose-responses is equally – and in some cases, arguably more - important (Calabrese EJ, 2013a), which reiteratively suggests and supports the need for continued, and more detailed research.

DISCUSSION

Assessment of Possible Parkinson's Disease Therapeutic Agents via Hormesis

A number of agents can significantly reduce damage in PD models when administered prior or concomitant to the stressing agent. As well, studies have shown some prevention or mitigation of PD-like effects when the potentially protective treatment was administered after the stressor agent (i.e.- a type of post- conditioning; Kim et al., 1998). However, there is insufficient experimental research to offer general conclusions on this latter effect. A diversity of agents are capable of affording neuroprotective effects, inclusive of both specific single compounds and complex mixtures. Regardless of the treatment or mechanisms (e.g.- GSH increase, ATP stabilization/increase), the maximum extent of protection, and the patterns of response exhibited were similar to qualitative and quantitative features of the hormetic biphasic dose-response.

There was one study in which vasoactive intestinal peptide (VIP) was employed as chemo-protective pretreatment to prevent damage from two stressor compounds (i.e., salsolinol and rotenone) that were simultaneously administered (Qualls et al., 2014). In this study, pre-treatment prevented damage induced by both agents in a pattern consistent with the hormetic dose-response. However, another paper revealed that salsolinol protected against rotenone but not 6-OHDA (Offen et al.,2000). Yet, in another study on the treatment of nicotine and donapenzil an additive protective response was observed (Das and Tizabi, 2009). It is interesting to note that many of the agents that offer protection against damage in multiple PD models have also been evaluated for their capacity to affect other neurodegenerative diseases (e.g, - AD and Huntington's disease), often with comparable success - especially when the underlying mechanism appears to involve up-regulation of antioxidant responses (e.g. - increases in GSH and ATP). These findings suggest that by exerting hormetic responses, several agents may have potential to prevent or reduce PD-like effects. These agents produced stimulatory effects in the range of 30-60%, and produced inhibition at higher doses. The effective dose range was found to be highly variable. This variability is important, as the optimal dose may be relatively close to a (high) dose that is ineffective and/or toxic. Given the often considerable inter-individual diversity in response to pharmacological agents, this variability in dose range would need to be considered and evaluated in any attempt to translate experimental

findings to clinical applications. .

Hormesis and Resilience: Toward a Broader Perspective, Goal, and Role.

We maintain that findings demonstrating the activity and mechanisms of hormetic dose-responses warrant further consideration. Hormetic mechanisms may be operative in, and therefore might be clinically accessed for induction of biological resilience. Resilience, the ability to adequately respond to allostatic loads and perturbations**,** is regarded as a fundamental component of positive adaptability in dynamic, non-linear biological systems (Holling. 1973; Holland, 1992). Multiple factors, (e.g.- genetics, environment, trauma) during prenatal and adolescent development have been shown to both affect and be affected by the capacity for resilience, and to influence health and susceptibility to disease and dysfunction (Gallopin, 2006; McEwen, 2003; Varadhan et al. 2008). Thus, there is increasing interest in gaining improved understanding of cellular mechanisms of resilience, and to translate this knowledge into approaches toward promoting health and resistance to insult and injury. Cellular resilience entails metabolic and signaling mechanisms that enable recovery and adaptive processes following stress.

Resilient phenotypes will typically conform to the quantitative and temporal features of the hormetic dose-time response relationship, often within a preconditioning context. While the amplitude of induced resilience is modest, such processes may incur relatively durable effects as a consequence of the type and extent of preconditioning (Gidday, 2015). We propose that such hormetic responses may be important to improving clinical approaches to neurodegenerative disorders. For example, given that the onset and progression of PD are age dependent, engaging preconditioning methods “early and often” may provee to be of value in individuals who have been identified with disease diatheses, and/or who are in prodromal or early phases of the disease process. This is of note given that preconditioning-induced hormetic resilience has been shown to decrease with age in a variety of animal models (although some success has been achieved in

restoring these functions via exercise , dietary modification, and pharmacological interventions; Calabrese et al., 2015; Calabrese, 2016c).

The question remains as to whether, and to what extent preconditioning methods can and should be used in the treatment of PD and other neurodegenerative conditions. As well, it will be important to further explore and define those ways that hormetic responses can be engaged to optimize function and protection in neural systems, so as to maximize the effectiveness of existing and newly developing therapeutics (e.g.-novel pharmacological agents; non-invasive and invasive brain stimulation). To date, the pharmacological treatment of PD is still mostly reliant upon the use of levodopa, some fifty years after its introduction for the therapeutic management of Parkinsonian patients. Levodopa therapy is characterized by a strong symptomatic effect on motor symptoms and, at certain levels, could act following hormetic properties. For instance, the possibility to induce and maintain the so-called "long-duration response"(Quattrone et al., 1995; Zappia et al.,1999) that is a sustained clinical benefit appearing days or weeks after beginning the treatment, is mainly due to the administration of low cumulative doses of levodopa, whereas higher dosages may have detrimental effects (Zappia et al., 2000). Furthermore, it is well known that levodopa may influence complex cognitive functions, such as working memory and cognitive control that are mediated by mesocortical dopaminergic pathways (Miller and Cohen, 2001). Additionally, the effects of levodopa could be recognized as a hormetic-U-shaped dose-response, in light of the (low dose-induced) improvements as well as (high dose-induced) impairments observed (Cools and D'Esposito, 2011).

Recent research demonstrates that neuroinflammatory events play a critical role in the progression of PD. Such processes involve activated pro-inflammatory microglial M1 phenotype via cytokine production. Studies have shown that progression of PD can be mitigated and in some instances reversed via neuroprotective agents (e.g.donepezil; rosiglitazone) that exert hormetic dose-responses to induce microglia to express and sustain the anti-inflammatory M2 phenotype (Chen et al., 2015; Pisanu et al., 2014)]. Moreover, hormetic bi-phasic dose-responses may be involved in the process of macrophage reprogramming and polarization that is produced by

chemicals, as well as ionizing radiation (Walton, 2017; Genard et al., 2017; Wu et al., 2017). Other studies have shown that preconditioning-induced protection responses are associated with increased M2 polarization across multiple organs/cell types (e.g., bone – Young et al., 2009; spinal cord – Hayakawa et al., 2014; mesenchymal stem cells – Lin et al., 2017, Mountziaris et al 2010; Kidney – Hato et al., 2015) reflecting the generality of the adaptive strategy. These findings suggest that hormetic mechanisms may play a role in mediating M1 or M2 macrophagic cell (e.g.- microglial) phenotypes that respectively mediate pro- and/or anti-inflammatory functions that are likely operative in pathologic and adaptive processes.

We propose that further studies of hormesis, preconditioning, and resilience will be vital to ongoing international efforts in translational neuroscience (e.g.- the European Union Human Brain Project, US Brain Research through Advancing Innovative Neurotechnology –BRAIN – initiative; China Brain Project; etc.) that are focused, to some extent, upon improving diagnosis, treatment and/or prevention of neuropsychiatric disease and injury. Indeed, a further understanding of hormesis may foster increased capability to harness subtle, yet potent mechanisms of physiological adaptation, which may enable a synergistic approach to clinical intervention(s) to allow more effective, efficient and affordable care. The integration, optimization, and personalization of such treatments pose both a challenge and opportunity to the biomedical sciences and clinical medicine, to which our group remains dedicated.

AUTHORS' CONTRIBUTIONS

All authors had full access to the study and take responsibility for the integrity and the accuracy of the study concept and design. Drafting of the manuscript: VC, AS, ATS, SM, MS, FA, DM, JG, MZ, CF, EJC. Critical revision of the manuscript for important intellectual content: VC, EJC and JG. Study supervision: VC and EJC. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

There is no Conflict of Interest to declare

Footnote 1: The data used to construct the figures of hormetic dose responses were obtained via a search of the current (2018) hormesis database (Calabrese and Blain, 2005, 2011). These two references provide the reader with a detailed description of the methodology of the evaluative criteria (e.g., study design, statistical analysis, study replication criteria and other criteria), and a description of the nearly 40 fields of information obtained from each of the dose response entries into the hormesis database (Calabrese and Blain, 2005, 2011). The hormesis database is continuously expanded on a weekly basis. The database has been complemented with several other hormesis databases designed to estimate the frequency of hormesis in the toxicological and pharmacological literature via the use of a priori and evaluative criteria (Calabrese and Baldwin 2003; Calabrese et al., 2006, 2008, 2010).

REFERENCES

Abdanipour A, Tiraihi T, Noori-Zadeh A, Majdi A, Gosaili R. 2014. Evaluation of lovastatin effects on expression of anti-apoptotic Nrf2 and PGC-1alpha genes in neural stem cells treated with hydrogen peroxide. *Mol Neurobiol* 49(3) : 1364-72.

Ba F, Pang PK, Davidge ST, Benishin CG. 2004. The neuroprotective effects of estrogen in SK-N-SH neuroblastoma cell cultures. *Neurochem Int* 44(6) : 401-11.

Blandini F, Armentero MT, Fancellu R, Blaugrund E, Nappi G. 2004. Neuroprotective effect of rasagiline in a rodent model of Parkinson's disease. *Exp Neurol* 187(2) : 455-9.

Calabrese EJ. 2008a. Hormesis and medicine. *Br J Clin Pharmacol* 66(5) : 594-617.

Calabrese EJ. 2008b. Pharmacological enhancement of neuronal survival. *Crit Rev Toxicol* 38(4) : 349-89.

Calabrese EJ. 2008c. Neuroscience and hormesis: overview and general findings. *Crit Rev Toxicol* 38(4):249-252.

Calabrese EJ. 2008d. Dose-response features of neuroprotective agents: An integrative summary. *Crit Rev Toxicol* 38(4):253-348.

Calabrese EJ. 2008e. Enhancing and regulating neurite outgrowth. *Crit Rev Toxicol* 38(4):391-418.

Calabrese EJ. 2011. Toxicology rewrites its history and rethinks its future: giving equal focus to both harmful and beneficial effects. *Environ Toxicol Chem* 30(12): 2658-73.

Calabrese EJ. 2011. Toxicology rewrites its history and rethinks its future: giving equal focus to both harmful and beneficial effects. *Environ Toxicol Chem* 30(12): 2658-73.

Calabrese EJ. 2013a. Hormetic mechanisms. *Crit Rev Toxicol* 43(7): 580-606.

Calabrese EJ. 2013b. The hormetic dose response often describes drug therapies for stroke and traumatic brain injury. In: Giordano J, Waters P. (eds.) *Brain Injury: Spectrum Effects and Implications*. Arlington: Potomac Institute Press, pp. 221-253.

Calabrese EJ. 2013c. Biphasic dose responses in biology, toxicology and medicine: Accounting for their generalizability and quantitative features. *Env Poll* 182:452-460.

Calabrese EJ. 2015. Historical foundations of hormesis. *Homeopathy* 104(2): 83-9.

Calabrese EJ. 2016a. Preconditioning is hormesis part I: Documentation, dose-response features and mechanistic foundations. *Pharmacol Res* 110 : 242-64.

Calabrese EJ. 2016b. Preconditioning is hormesis part II: How the conditioning dose mediates protection: Dose optimization within temporal and mechanistic frameworks. *Pharmacol Res* 110 : 265-75.

Calabrese EJ. 2016c. Pre- and post-conditioning hormesis in elderly mice, rats, and humans: its loss and restoration. *Biogerontology* 17(4) : 681-702.

Calabrese EJ, Baldwin LA. 2000a. Chemical hormesis: its historical foundations as a biological hypothesis. *Hum Exp Toxicol* 19(1): 2-31.

Calabrese EJ, Baldwin LA. 2000b. Tales of two similar hypotheses: the rise and fall of chemical and radiation hormesis. *Hum Exp Toxicol* 19(1) : 85-97.

Calabrese EJ, Baldwin LA. 2000. Radiation hormesis: the demise of a legitimate hypothesis. *Hum Exp Toxicol* 19(1) :76-84.

Calabrese EJ, Baldwin LA. 2000. Radiation hormesis: its historical foundations as a biological hypothesis. *Hum Exp Toxicol* 19(1) : 41-75.

Calabrese EJ, Baldwin LA. 2000. The marginalization of hormesis. *Hum Exp Toxicol* 19(1): 32-40.

Calabrese EJ, Baldwin LA. 2002. Defining hormesis. *Hum Exp Toxicol* 21(2): 91-7.

Calabrese EJ, Baldwin LA. 2001. The frequency of U-shaped dose responses in the toxicological literature. *Toxicol Sci* 62(2) : 330-8.

Calabrese EJ, Baldwin LA. 2003. The hormetic dose-response model is more common than the threshold model in toxicology. *Toxicol Sci* 71(2) : 246-50.

Calabrese EJ, Blain R. 2005. The occurrence of hormetic dose responses in the toxicological literature, the hormesis database: an overview. *Toxicol Appl Pharmacol* 202(3) : 289-301.

Calabrese EJ, Blain RB. 2011. The hormesis database: the occurrence of hormetic dose responses in the toxicological literature. *Regul Toxicol Pharmacol* 61(1) : 73-81.

Calabrese EJ, Mattson MP. 2011. Hormesis provides a generalized quantitative estimate of biological plasticity. *J Cell Comm Signal* 5(1):25-38.

Calabrese EJ, Dhawan G, Kapoor R, Iavicoli I, Calabrese V. 2015. What is hormesis and its relevance to healthy aging and longevity?. *Biogerontology* 16(6) :693-707.

Calabrese EJ, Staudenmayer JW, Stanek EJ, Hoffmann, GR. 2006. Hormesis outperforms threshold model in National Cancer Institute antitumor drug screening database. *Toxicol Sci* 94(2):368-378.

Calabrese E, Stanek EJ, Nascarella M, Hoffmann G. 2008. Hormesis predicts low-dose responses better than threshold models. *Int J Toxicol* 5:369-378.

Calabrese V, Cornelius C, Stella AM, Calabrese EJ. 2010a. Cellular stress responses, mitostress and carnitine insufficiencies as critical determinants in aging and neurodegenerative disorders: role of hormesis and vitagenes. *Neurochem Res* 35(12) : 1880-915.

Calabrese EJ, Hoffmann GR, Stanek EJ, Nascarella MA. 2010b. Hormesis in high-throughput screening of antibacterial compounds in E coli. *Hum Exper Toxicol* 8:667-677.

Calabrese EJ, Calabrese V, Giordano J. 2017. The role of hormesis in the functional performance and protection of neural systems. *Brain Circ* 3:1013.

Carradori S, Silvestri R. 2015. New Frontiers in Selective Human MAO-B Inhibitors. *J Med Chem* 58(17): 6717-32.

Chen JH, Ou HP, Lin CY, Lin FJ, Wu CR, Chang SW, Tsai CW. 2012. Carnosic acid prevents 6-hydroxydopamine-induced cell death in SH-SY5Y cells via mediation of glutathione synthesis. *Chem Res Toxicol* 25(9) : 1893-901.

Chen T, Hou R, Xu S, Wu C. 2015. Donepezil regulates 1-methyl-4-phenylpyridinium-induced microglial polarization in Parkinson's disease. *ACS Chem Neurosci* 6:1708-1714.

Choi JG, Kim HG, Kim MC, Yang WM, Huh Y, Kim SY, Oh MS. 2011. Polygalae radix inhibits toxin-induced neuronal death in the Parkinson's disease models. *J Ethnopharmacol* 134(2) : 414-21.

Choi MJ, Choi BT, Shin HK, Shin BC, Han YK, Baek JU. 2015. Establishment of a comprehensive list of candidate antiaging medicinal herb used in korean medicine by text mining of the classical

korean medical literature, "dongeuibogam," and preliminary evaluation of the antiaging effects of these herbs. *J Evid Based Complementary Altern Med* eCAM 2015 : 873185.

Cools R, D'Esposito M. 2011. Inverted-U-shaped dopamine actions on human working memory and cognitive control. *Biol Psychiatry* 69(12) : e113-25.

Cunha MP, Martin-de-Saavedra MD, Romero A, Parada E, Egea J, Del Barrio L, Rodrigues AL, Lopez MG. 2013. Protective effect of creatine against 6-hydroxydopamine-induced cell death in human neuroblastoma SH-SY5Y cells: Involvement of intracellular signaling pathways. *Neuroscience* 238 :185-94.

Das JR, Tizabi Y. 2009. Additive protective effects of donepezil and nicotine against salsolinol-induced cytotoxicity in SH-SY5Y cells. *Neurotox Res* 16(3): 194-204.

Doo AR, Kim SN, Park JY, Cho KH, Hong J, Eun-Kyung K, Moon SK, Jung WS, Lee H, Jung JH, Park HJ. 2010a. Neuroprotective effects of an herbal medicine, Yi-Gan San on MPP+/MPTP-induced cytotoxicity in vitro and in vivo. *J Ethnopharmacol* 131(2) : 433-42.

Doo AR, Kim ST, Kim SN, Moon W, Yin CS, Chae Y, Park HK, Lee H, Park HJ. 2010b. Neuroprotective effects of bee venom pharmaceutical acupuncture in acute 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced mouse model of Parkinson's disease. *Neurol Res* 32 Suppl 1 : 88-91.

El Ayadi A, Zigmond MJ. 2011. Low concentrations of methamphetamine can protect dopaminergic cells against a larger oxidative stress injury: mechanistic study. *PloS one* 6(10) : e24722.

El-Ghazaly MA, Sadik NA, Rashed ER, Abd-El-Fattah AA. 2015. Neuroprotective effect of EGb761(R) and low-dose whole-body gamma-irradiation in a rat model of Parkinson's disease. *Toxicol Ind Health* 31(12) : 1128-43.

Feng Y, Liu T, Li XQ, Liu Y, Zhu XY, Jankovic J, Pan TH, Wu YC. 2014.Neuroprotection by Orexin-A via HIF-1alpha induction in a cellular model of Parkinson's disease. *Neurosci. Lett* 579 (2014) 35-40.

Fu RH, Wang YC, Chen CS, Tsai RT, Liu SP, Chang WL, Lin HL, Lu CH, Wei JR, Wang ZW, Shyu WC, Lin SZ. 2014. Acetylcorynoline attenuates dopaminergic neuron degeneration and alpha-synuclein aggregation in animal models of Parkinson's disease. *Neuropharmacology* 82 : 108-20.

Galan-Rodriguez B, Suarez J, Gonzalez-Aparicio R, Bermudez-Silva FJ, Maldonado R, Robledo P, Rodriguez de Fonseca F, Fernandez-Espejo E. 2009. Oleoylethanolamide exerts partial and dose-dependent neuroprotection of substantia nigra dopamine neurons. *Neuropharmacology* 56(3) (2009) 653-64.

Gallopin GC. 2006. Linkages between vulnerability, resilience and adaptive capacity. *Global Environ Change* 16(3): 293-303.

Gassen M, Gross A, Youdim MB. 1998a. Apomorphine enantiomers protect cultured pheochromocytoma (PC12) cells from oxidative stress induced by H2O2 and 6-hydroxydopamine. *Mov Disord* 13(4): 661-7.

Gassen M, Pinchasi B, Youdim MB. 1998b. Apomorphine is a potent radical scavenger and protects cultured pheochromocytoma cells from 6-OHDA and H2O2-induced cell death. *Adv Pharmacol* 42 : 320-4.

Genard G, Lucas S, Michiels C. 2017. Reprogramming of tumor-associated macrophages with anticancer therapies: Radiotherapy versus chemo- and immunotherapies. *Front Immunol* Volume 8, article 828.

Gidday JM. 2015. Extending injury- and disease-resistant CNS phenotypes by repetitive epigenetic conditioning. *Front Neurol* 6 : 42.

Gille G, Rausch WD, Hung ST, Moldzio R, Ngyuen A, Janetzky B, Engfer A, Reichmann H. 2002a. Protection of dopaminergic neurons in primary culture by lisuride. *J Neural Transm* 109(2) : 157-69.

Gille G, Rausch WD, Hung ST, Moldzio R, Janetzky B, Hundemer HP, Kolter T, Reichmann H. 2002b. Pergolide protects dopaminergic neurons in primary culture under stress conditions. *J Neural Transm* 109(5-6) 633-43.

Gille G, Radad K, Reichmann H, Rausch WD. 2006. Synergistic effect of alpha-dihydroergocryptine and L-dopa or dopamine on dopaminergic neurons in primary culture. *J Neural Transm* 113(9) : 1107-18.

Guo DJ, Li F, Yu PH, Chan SW. 2013. Neuroprotective effects of luteolin against apoptosis induced by 6-hydroxydopamine on rat pheochromocytoma PC12 cells. *Pharm Biol* 51(2) : 190-6.

Gunjima K, Tomiyama R, Takakura K, Yamada T, Hashida K, Nakamura Y, Konishi T, Matsugo S, Hori O. 2014. 3,4-dihydroxybenzalacetone protects against Parkinson's disease-related neurotoxin 6-OHDA through Akt/Nrf2/glutathione pathway. *J Cell Biochem* 115(1) : 151-60.

Grunblatt E, Mandel S, Berkuzki T, Youdim MB. 1999. Apomorphine protects against MPTP-induced neurotoxicity in mice. *Mov Disord* 14(4) : 612-8.

Hamann J, Wernicke C, Lehmann J, Reichmann H, Rommelspacher H, Gille G. 2008. 9-Methyl-beta-carboline up-regulates the appearance of differentiated dopaminergic neurones in primary mesencephalic culture. *Neurochem Int* 52(4-5) : 688-700.

Hara H, Kamiya T, Adachi T. 2011. Endoplasmic reticulum stress inducers provide protection against 6-hydroxydopamine-induced cytotoxicity. *Neurochem Int* 58(1) : 35-43.

Hato T, Winfree S, Kalakeche R, Dube S, Kumar R, Yoshimoto M, Plotkin Z, Dagher PC. 2015. The macrophage mediates the renoprotective effects of endotoxin preconditioning. *J Am Soc Nephrol* 26:1347-1362.

Hayakawa K, Okazaki R, Morioka K, Nakamura K, Tanaka S, Ogata T. 2014. Lipopolysaccharide preconditioning facilitates M2 activation of resident microglia after spinal cord injury. *J Neurosci Res* 92:1647-1658.

He AY, Qiu LJ, Gao Y, Zhu Y, Xu ZW, Xu JM, Zhang ZH. 2011. The role of oxidative stress in neuromelanin synthesis in PC12 cells. *Neuroscience* 189 : 43-50.

Holland JH. 1992. *Adaptation in Natural and Artificial Systems*. Cambridge, MA: MIT Press.

Holling CS. 1973. Resilience and stability in ecological systejms. *Ann Rev Ecol Systematics* 4:1-23.

Huleatt PB, Khoo ML, Chua YY, Tan TW, Liew RS, Balogh B, Deme R, Goloncser F, Magyar K,

Sheela DP, Ho HK, Sperlagh B, Matyus P, Chai CL. 2015.Novel arylalkenylpropargylamines as neuroprotective, potent, and selective monoamine oxidase B inhibitors for the treatment of Parkinson's disease. *J Med Chem* 58(3): 1400-19.

Keller J, Owens CT, Lai JC, Devaud LL. 2005. The effects of 17beta-estradiol and ethanol on zinc- or manganese-induced toxicity in SK-N-SH cells. *Neurochem Int* 46(4) : 293-303.

Kim HS, Hong YT, Oh KW, Seong YH, Rheu HM, Cho DH, Oh S, Park WK, Jang CG. 1998. Inhibition by ginsenosides Rb1 and Rg1 of methamphetamine-induced hyperactivity, conditioned place preference and postsynaptic dopamine receptor supersensitivity in mice. *Gen Pharmaco* 30(5) : 783-9.

Kim YC, Kim SR, Markelonis GJ, Oh TH. 1998. Ginsenosides Rb1 and Rg3 protect cultured rat cortical cells from glutamate-induced neurodegeneration. *J Neurosci Res* 53(4) : 426-32.

Kim HG, Ju MS, Shim JS, Kim MC, Lee SH, Huh Y, Kim SY, Oh MS. 2010. Mulberry fruit protects dopaminergic neurons in toxin-induced Parkinson's disease models. *Br J Nutr* 104(1) : 8-16.

Kim DW, Lee KT, Kwon J, Lee HJ, Lee D, Mar W. 2015. Neuroprotection against 6-OHDA-induced oxidative stress and apoptosis in SH-SY5Y cells by 5,7-Dihydroxychromone: Activation of the Nrf2/ARE pathway. *Life sciences* 130 : 25-30.

Kim YH, Beak SH, Charidimou A, Song M. 2016. Discovering New Genes in the Pathways of Common Sporadic Neurodegenerative Diseases: A Bioinformatics Approach. *J Alzheimers Dis* 51(1) 293-312.

Kojima S, Matsuki O, Nomura T, Yamaoka K, Takahashi M, Niki E. 1999. Elevation of antioxidant potency in the brain of mice by low-dose gamma-ray irradiation and its effect on 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced brain damage. *Free Radic Biol Med* 26(3-4): 388-95.

Lee CH, Hwang DS, Kim HG, Oh H, Park H, Cho JH, Lee JM, Jang JB, Lee KS, Oh MS. 2010. Protective effect of Cyperi rhizoma against 6-hydroxydopamine-induced neuronal damage. *J Med Food* 13(3) : 564-71.

Levites Y, Amit T, Youdim MB, Mandel S. 2002. Involvement of protein kinase C activation and cell survival/ cell cycle genes in green tea polyphenol (-)-epigallocatechin 3-gallate neuroprotective action. *J Biol Chem* 277(34) : 30574-80.

Li J, Le W. 2013. Modeling neurodegenerative diseases in Caenorhabditis elegans. *Exp Neurol* 250 : 94-103.

Liang Y, Li S, Zou Q, Su B. 2006. Potential neuroprotective effect of low dose whole-body gamma-irradiation against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced dopaminergic toxicity in C57 mice. *Neurosci Lett* 400(3): 213-7.

Lin T, Pajarinen J, Nabeshima A, Lu L, Nathan K, Jamsen E, Yao Z, Goodman SB. 2017. Preconditioning of murine mesenchymal stem cells synergistically enhanced immunomodulation and osteogenesis. *Stem Cell Res & Ther* 8:277

Liu H, Mao P, Wang J, Wang T, Xie CH. 2015. Allicin Protects PC12 Cells Against 6-OHDA-Induced Oxidative Stress and Mitochondrial Dysfunction via Regulating Mitochondrial Dynamics. *Cell Physiol Biochem* 36(3) : 966-79.

Liu J, Su H, Qu QM. 2016. Carnosic Acid Prevents Beta-Amyloid-Induced Injury in Human Neuroblastoma SH-SY5Y Cells via the Induction of Autophagy. *Neurochem Res* 41(9) : 2311-23.

Lo YC, Liu Y, Lin YC, Shih YT, Liu CM, Burka LT. 2008. Neuronal effects of 4-t-Butylcatechol: a model for catechol-containing antioxidants. *Toxicol Appl Pharmacol* 228(2) : 247-55.

Lo YC, Shih YT, Tseng YT, Hsu HT. 2012. Neuroprotective Effects of San-Huang-Xie-Xin-Tang in the MPP(+)/MPTP Models of Parkinson's Disease In Vitro and In Vivo. J *Evid Based Complementary Altern Med* eCAM 2012 : 501032.

Magalingam KB, Radhakrishnan A, Haleagrahara N. 2013. Rutin, a bioflavonoid antioxidant protects rat pheochromocytoma (PC-12) cells against 6-hydroxydopamine (6-OHDA)-induced neurotoxicity. *Int J Mol Med* 32(1) : 235-40.

Magalingam KB, Radhakrishnan A, Haleagrahara N. 2014. Protective effects of flavonol isoquercitrin, against 6-hydroxy dopamine (6-OHDA)-induced toxicity in PC12 cells. *BMC Res*

Notes 7 : 49.

Matthews RT, Ferrante RJ, Klivenyi P, Yang L, Klein AM, Mueller G, Kaddurah-Daouk R, Beal MF. 1999. Creatine and cyclocreatine attenuate MPTP neurotoxicity. *Exp Neurol* 157(1) : 142-9.

Mattson MP. 2008. Hormesis defined. *Ageing Res Rev* 7(1): 1-7.

McEwen BS. 2003. Interacting mediators of allstasis and allostatic lad: towards an understnading of resilience in aging. *Metabolism* 52(2): 10-16.

Mena MA, Davila V, Sulzer D. 1997. Neurotrophic effects of L-DOPA in postnatal midbrain dopamine neuron/cortical astrocyte cocultures. *J Neurochem* 69(4) : 1398-408.

Miller EK, Cohen JD. 2001. An integrative theory of prefrontal cortex function. *Annu Rev Neurosci* 24 : 167-202.

Mountziaris PM, Tzouanas S, Mikos AG. 2010. Dose effect of tumor necrosis factor-a *in vitro* osteogenic differentiation of mescenchymal stem cellson biodegradable polymeric microfiber scaffolds. *Biomaterials* 31(7):1666.

Mozdzen E, Kajta M, Wasik A, Lenda T, Antkiewicz-Michaluk L. 2015. Salsolinol, an endogenous compound triggers a two-phase opposing action in the central nervous system. *Neurotox Res* 27(3) : 300-13.

Nie G, Cao Y, Zhao B. 2002. Protective effects of green tea polyphenols and their major component, (-)-epigallocatechin-3-gallate (EGCG), on 6-hydroxydopamine-induced apoptosis in PC12 cells. *Redox report : communications in free radical research* 7(3) : 171-7.

Niering P, Michels G, Watjen W, Ohler S, Steffan B, Chovolou Y, Kampkotter A, Proksch P, Kahl R. 2005. Protective and detrimental effects of kaempferol in rat H4IIE cells: implication of oxidative stress and apoptosis. *Toxicol Appl Pharmacol* 209(2) : 114-22.

Offen D, Ziv I, Sternin H, Melamed E, Hochman A. 1996. Prevention of dopamine-induced cell death by thiol antioxidants: possible implications for treatment of Parkinson's disease. *Exp Neurol* 141(1) : 32-9.

Offen D, Sherki Y., Melamed , Fridkin M, Brenneman DE, Gozes I. 2000. Vasoactive intestinal

peptide (VIP) prevents neurotoxicity in neuronal cultures: relevance to neuroprotection in Parkinson's disease. *Brain Res* 854(1-2) :257-62.

Park YH, Son IH, Kim B, Lyu YS, Moon HI, Kang HW. 2009. Poria cocos water extract (PCW) protects PC12 neuronal cells from beta-amyloid-induced cell death through antioxidant and antiapoptotic functions. *Pharmazie* 64(11) : 760-4.

Perez HJ, Carrillo SC, Garcia E, Ruiz-Mar G, Perez-Tamayo R, Chavarria A. 2014. Neuroprotective effect of silymarin in a MPTP mouse model of Parkinson's disease. *Toxicology* 319 : 38-43.

Pisanu A, Lecca D, Mulas G, Wardas J, Simbula G, Spiga S, Carta AR. 2014. Dynamic changes in pro- and anti-inflammatory cytokines in microglia after PPAR-*y* agonist neuroprotective treatment in the MPTPp mouse model of progressive Parkinson's disease. *Neurobiol Dis* 71:280-291.

Qualls Z, Brown D, Ramlochansingh C, Hurley LL, Tizabi Y. 2014. Protective effects of curcumin against rotenone and salsolinol-induced toxicity: implications for Parkinson's disease. *Neurotox Res* 25(1) : 81-9.

Quattrone A, Zappia M, Aguglia U, Branca D, Colao R, Montesanti R, Nicoletti G, Palmieri A, Parlato G, Rizzo M. 1995. The subacute levodopa test for evaluating long-duration response in Parkinson's disease. *Ann Neurol* 38(3) : 389-95.

Radad K, Moldzio R, Taha M, Rausch WD. 2009. Thymoquinone protects dopaminergic neurons against MPP+ and rotenone. *Phytother Res* 23(5) : 696-700.

Radad K, Scheller D, Rausch WD, Reichmann H, Gille G. 2014. Neuroprotective effect of rotigotine against complex I inhibitors, MPP(+) and rotenone, in primary mesencephalic cell culture, *Folia Neuropathol* 52(2) : 179-86.

Radad K, Moldzio R, Rausch WD. 2015. Rapamycin protects dopaminergic neurons against rotenone-induced cell death in primary mesencephalic cell culture. *Folia Neuropathol* 53(3): 250-61.

Radad K, Gille G, Xiaojing J, Durany N, Rausch WD. 2017. CDP-choline reduces dopaminergic

cell loss induced by MPP(+) and glutamate in primary mesencephalic cell culture. *Int J Neurosci* 117(7) : 985-98.

Rattan SI, Fernandes RA, Demirovic D, Dymek B, Lima CF. 2009. Heat stress and hormetin-induced hormesis in human cells: effects on aging, wound healing, angiogenesis, and differentiation. *Dose-response* 7(1) : 90-103.

Ryan RE, Ross SA, Drago J, Loiacono RE. 2001. Dose-related neuroprotective effects of chronic nicotine in 6-hydroxydopamine treated rats, and loss of neuroprotection in alpha4 nicotinic receptor subunit knockout mice. *Br J Pharmacol* 132(8): 1650-6.

Ryan RE, Loiacono RE. 2001. Nicotine regulates alpha7 nicotinic receptor subunit mRNA: implications for nicotine dependence. *Neuroreport* 12(3) : 569-72.

Segev-Amzaleg N, Trudler D, Frenkel D. 2013. Preconditioning to mild oxidative stress mediates astroglial neuroprotection in an IL-10-dependent manner. *Brain Behav Immun* 30 : 176-85.

Shulman LM, Taback RL, Bean J, Weiner WJ. 2001. Comorbidity of the nonmotor symptoms of Parkinson's disease. *Mov Disord* 16(3) : 507-10.

Singh M, Murthy V, Ramassamy C. 2013. Neuroprotective mechanisms of the standardized extract of Bacopa monniera in a paraquat/diquat-mediated acute toxicity. *Neurochem Int* 62(5) : 530-9.

Soliman AM, Fathalla AM, Moustafa AA. 2016. Dose-dependent neuroprotective effect of caffeine on a rotenone-induced rat model of parkinsonism: A histological study. *Neurosci Lett* 623 : 63-70.

Sonsalla PK, Wong LY, Harris SL, Richardson JR, Khobahy I, Li W, Gadad BS, German DC. 2012. Delayed caffeine treatment prevents nigral dopamine neuron loss in a progressive rat model of Parkinson's disease. *Exp Neurol* 234(2) : 482-7.

Tian LL, Zhou Z, Zhang Q, Sun YN, Li CR, Cheng CH, Zhong ZY, Wang SQ. 2007. Protective effect of (+/-) isoborneol against 6-OHDA-induced apoptosis in SH-SY5Y cells. *Cell Physiol Biochem* 20(6) : 1019-32.

Tiong CX, Lu M, Bian JS. 2010. Protective effect of hydrogen sulphide against 6-OHDA-induced cell injury in SH-SY5Y cells involves PKC/PI3K/Akt pathway. *Br J Pharmacol 161(2) : 467-80.*

Vaglini F, Pardini C, Viaggi C, Caramelli A, Corsini GU. 2008. Apomorphine offers new insight into dopaminergic neuron vulnerability in mesencephalic cultures *Neuropharmacology* 55(5) : 737-42.

Varadhan R, Seplaki CL, Xue QL, Bandeen-Roche K, Fried LP. 2008. Stimulus-rsponse paradigm for characterizing loss of resilience in homeostatic regulation associated with frailty. *Mech Ageing Devel* 129(11): 666-670.

Walton EL. (2017). Radiotherapy and the tumor microenvironment: the "macro" picture. *Biomed J* 40:185-188.

Wang L, Xu S, Xu X, Chan P. 2009. (-)-Epigallocatechin-3-Gallate protects SH-SY5Y cells against 6-OHDA-induced cell death through STAT3 activation. *J Alzheimers Dis* 17(2) : 295-304.

Wu Q, Allouch A, Martins I, Modjtahedi N, Deutsch E, Perfettini J-L. 2017. Macrophage biology plays a central role during ionizing radiation-elicited tumor response. *Biomed J* 40:200-211.

Xiao-Qing T, Jun-Li Z, Yu C, Jian-Qiang F, Pei-Xi C. 2005. Hydrogen peroxide preconditioning protects PC12 cells against apoptosis induced by dopamine. *Life Sci J* 78(1) : 61-6.

Young S, Patel ZS, Kretlow JD, Murphy MB, Mountziaris PM, Baggett LS, Ueda H, Tabata Y, Jansen JA, Wong M, Mikos AG. 2009. Dose effects of dual delivery of vascular endothelial growth factor and bone morphogenetic protein-2 on bone regeneration in a rat critical-size defect model. *Tiss Eng* Part A 15(9):2347-2362.

Yuyun X, Jinjun Q, Minfang X, Jing Q, Juan X, Rui M, Li Z, Jing G. 2013. Effects of Low Concentrations of Rotenone upon Mitohormesis in SH-SY5Y Cells. *Dose-response : a publication of International Hormesis Society* 11(2) : 270-80.

Zappia M, Bosco D, Plastino M, Nicoletti G, Branca D, Oliveri RL, Aguglia U, Gambardella A, Quattrone A. 1999. Pharmacodynamics of the long-duration response to levodopa in PD. *Neurology* 53(3) : 557-60.

Zappia M, Oliveri RL, Bosco D, Nicoletti G, Branca D, Caracciolo M, Napoli ID, Gambardella A, Quattrone A. 2000. The long-duration response to L-dopa in the treatment of early PD. *Neurology*

54(10) : 1910-5.

Zhang Y, Li S, Liang Y, Wen C, Guo Q, Su B. 2009. Potential mechanisms of neuroprotection induced by low dose total-body gamma-irradiation in C57 mice administered with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). *Neurosci Lett* 450(2) : 106-10.

Zhang G, Xiong N, Zhang Z, Liu L, Huang J, Yang J, Wu J, Lin Z, Wang T. 2015. Effectiveness of traditional Chinese medicine as an adjunct therapy for Parkinson's disease: a systematic review and meta-analysis. *PloS one* 10(3) : e0118498.

Zhang C, Li C, Chen S, Li Z, Jia X, Wang K, Bao J, Liang Y, Wang X, Chen M, Li P, Su H, Wan JB, Lee SM, Liu K, He C. 2017a. Berberine protects against 6-OHDA-induced neurotoxicity in PC12 cells and zebrafish through hormetic mechanisms involving PI3K/AKT/Bcl-2 and Nrf2/HO-1 pathways. *Redox Biol* 11 : 1-11.

Zhang C, Li C, Chen S, Li Z, Ma L, Jia X, Wang K, Bao J, Liang Y, Chen M, Li P, Su H, Lee SM, Liu K, Wan JB, He C. 2017b. Hormetic effect of panaxatriol saponins confers neuroprotection in PC12 cells and zebrafish through PI3K/AKT/mTOR and AMPK/SIRT1/FOXO3 pathways. *Sci Rep* 7 : 41082.

Zhong SY, Chen YX, Fang M, Zhu XL, Zhao YX, Liu XY. 2014. Low-dose levodopa protects nerve cells from oxidative stress and up-regulates expression of pCREB and CD39. *PloS one* 9(4) : e95387.

Zhou M, Xu SL, Chen B. 2009. Dual effects of different concentrations of alpha-synuclein on the neurotoxicity of 6-hydroxydopamine in SH-SY5Y cells. *Sheng li xue bao : [Acta physiologica Sinica]* 61(4) : 324-30.

Zhou YF, Li WT, Han HC, Gao DK, He XS, Li L, Song JN, Fei Z. 2014. Allicin protects rat cortical neurons against mechanical trauma injury by regulating nitric oxide synthase pathways. *Brain Res Bull* 100 : 14-21.

Zhou H, Feng L, Xu F, Sun Y, Ma Y, Zhang X, Liu H, Xu G, Wu X, Shen Y, Sun Y, Wu X, Xu Q. 2017. Berberine inhibits palmitate-induced NLRP3 inflammasome activation by triggering

autophagy in macrophages: A new mechanism linking berberine to insulin resistance improvement. *Biomed Pharmacother* 89: 864-874.

Table 1. Effect of therapeutic agents on Parkinson's disease model SK-N-SH: Width and amplitude of stimulation

Reference	**SK-N-SH Model**	**Dose Range (fold) Stimulatory Width**	**Amplitude (compared to control 100%)**
(Chen et al., 2012)	Carnosic Acid	30	140
(Cunha et al., 2013)	Creatine	50,000	155
(Qualls et al.,2014)	Curcumin: Salsonlinol	10	138
(Qualls et al.,2014)	Curcumin: Rotenone	10	140
(Das and Tizabi, 2009)	Donapezel	$\geq$ 20	212
(Ba et al., 2004; Wang et al., 2009)	EGCC	$\geq$ 10 (MTT); 100 (HtdR)	160 (MTT); 200 (HtdR)
(Ba et al., 2004)	Estrogen	10^6	160
(Tian et al., 2007)	Isobonol	125	16
(Zhou et al., 2009)	Lactocystin	10	135
(Feng et al., 2014)	OREA	135, 175, 175	> 4
(Lo et al., 2008)	TBC	1000	29 (J), 172
(Doo et al., 2010)	YGS	50	155

Table 2. Effect of therapeutic agents on Parkinson's disease model PC12: Width and amplitude of stimulation

Reference	**PC12**	**Dose Range (fold) Stimulatory Width**	**Amplitude (compared to control 100%)**
(Offen et al., 1996)	Antioxidants	≥ 10	160 (DTT); 275 (NAC), 275 (GSH)
(Gassen et al., 1998a)	Apomorphine	715	60 (J)
(Gassen et al., 1998b)	Apomorphine	14	200
(Zhang et al., 2017a)	Berberi	80 NPC, PC	125, 125
(Lee et al., 2010)	CRE	58	130
(Levites et al., 2002)	Green/Black Tea	50 (GT); ~10 (BT)	155 (GT); 175 (BT)
(Xiao-Qing et al., 2005)	H2O2	> 3	188
(Magalingam et al., 2014)	Isoquercitin	≥ 10	250
(Zhong et al., 2014)	L-Dopa	~30	195
(He et al., 2011)	Neuromelin	< 20	118
(Zhang et al., 2017)	PTS	~ 33, 66 PC	125, 233
(Magalingam et al., 2013)	Rutin	> 10	210

Table 3. Recovery dose response for studies with a limited dose response

Reference	**Agent**	**Net Increase Protective Response**	**Net (%)**	**Notes**
(Liu et al., 2015)	Allicin	45 -> 80	35	
(Lo et al., 2012)	SHXT	21 -> 67	46	
(Levites et al., 2002)	EGCC	40 -> 93	53	Protection drop off at higher dose
(Sonsalla et al.,2012)	Caffeine	50 -> 95	45	Protection drop off at higher dose
(Soliman et al., 2016)	Caffeine	60 -> 95	35	
(Fu et al., 2014)	Acetylccrynoline	50 ->95	45	
(Cunha et al., 2013)	Creatine	50 -> 80	30	
(Tiong et al., 2010)	Hydrogen Sulphide	48 -> 88	54	
(Grunblatt et al., 1999)	Apomorphine	32 (DA) -> 48; 43 (DOPAC) -> 58	16; 15	
(Hara et al., 2011)	Thapsigarin	50 -> 80	30	Protection drop off at higher dose
(Singh et al., 2013)	BM	55 -> 80	25	
(Guo et al., 2013)	Luteolin	50 -> 90	40	
(Park et al., 2009)	PCW	60 -> 85	25	
(Nie et al., 2002)	GTPs; EGCC	60 (GTPs) -> 95; 60 (EGCC) -> 95	35; 35	

Table 4. Hormesis recovery dose response

Reference	Agent	% of Original Control Value After Stress (at conclusion of experiment) Control Group	% of Original Control Value After Treatment with Protective and Stress Agents (at conclusion of experiment)	Relative Increase (%) Protective Response as Compared to Control Group (100%)
(Ryan and Loiacono, 2001)	Nicotine	41.6	81.5	196
(Kim et al.,1998)	Rb1	~20% (estimate)	76.2	381
(Kim et al.,1998)	Rb3	~20% (estimate)	67.3	336
(Lo et al., 2008)	TBC	50	92	184
(Qualls et al.,2014)	Curcumin	55 (Rotenone)	80	145
(Qualls et al.,2014)	Curcumin	55 (Salsotinol)	78	142
(El Ayadi and Zigmond , 2011)	Meth	58	90 (ATP)	155
(Zhang et al., 2017)	PTS	62	86	139
(Ba et al., 2004)	Estrogen	48	78 (B)	162
(Ba et al., 2004)	Estrogen	25	48 (C)	192
(Ba et al., 2004)	Estrogen	10	30 (D)	300
(Ba et al., 2004)	Estrogen	15	30 (E)	200
(Chen et al., 2012)	Carnosic	46	78	169
(Cunha et al., 2013)	Creatine	62	98	158
(Doo et al., 2010b)	YGS	50	80	160
(Galan-Rodriguez et al., 2009)	OEA	40	80	200
(Lee et al., 2010)	CRE	45	60	133
(Levites et al., 2002)	EGCG	33	52	157
(Perez et al., 2014)		5	22	462
(Tian et al., 2007)	Isoborneol	38	92	242
(Wang et al., 2009)	EGCG	50	76	152
(Wang et al., 2009)	EGCG	52	95 (H)	182
(Zhang et al.,2017)	Berberine	60	80	133
(Zhou et al., 2009)	Lactocystin	50	80	160

Table 5. Listing of hormetic Parkinson's disease treating agents

Agents	**References**
5,7-DHC	(Kim et al., 2015)
6-OHDA	(Lo et al., 2008)
9-me-BC	(Hamann et al., 2008)
α-DHEC	(Gille et al., 2006)
Allicin	(Zhou et al., (2014)
Antioxidants: GSH; NAC; DTT	(Offen et al., 1996)
Apomorphine	(Gassen et al., 1998a; Vaglini et al.,2008)
Berberine	(Zhou et al., 2017)
Black Tea	(Levites et al., 2002)
Carnosic acid	(Chen et al., 2012)
Citicoline	(Radad et al., 2007)
CRE/Cyperia rhizome	(Lee et al., 2010)
Creatine	(Cunha et al.,2013)
Curcumin	(Qualls et al., 2014)
Cyperi Rhizoma (CRE)	(Lee et al., 2010)
Dopamine	(Xiao-Qing et al., 2005)
Donepezil	(Das and Tizabi, 2009)
EGCG	(Wang et al., 2009)
Estrogen	(Ba et al., 2004)
Ginosen doside: Rb1; Rg3	(Kim et al., 1998)
Ginsenoside Rb	(Liu et al., 2015)
Glucose oxidase (GO)	(He et al., 2011)
Green/Black Tea Extracts	(Levites et al., 2002)
H2O2	(Xiao-Qing et al., 2005)
Hepad	(Choi et al., 2015)
Isoborneol	(Tian et al., 2007)
Isoquercitin	(Magalingam et al., 2014)

Table 5. Listing of hormetic Parkinson's disease treating agents (Continued)

Lactacystin	(Zhou et al., 2009)
L-DOPA	(Zhong et al., 2014)
Lisuride	(Gille et al., 2002a)
Lovastatin	(Abdanipour et al., 2014)
Methamphetamine	(El Ayadi and Zigmond, 2011)
Mulberry juice	(Kim et al., 2010)
Nicotine	(Ryan and Loiacono, 2001)
Oleoylethanolamide (OEA)	(Galan-Rodriguez et al., 2009)
Orexin-A	(Feng et al., 2014)
Pergolide	(Gille et al., 2002b)
PRE/Polygalae radix	(Choi et al., 2011)
PTS	(Zhang et al., 2017)
Rapamycin	(Radad et al.,2015)
Rotenone	(Yuyun et al., 2013)
Rotigotine	(Radad et al., 2014)
Rutin	(Magalingam et al., 2013)
Salsolinol	(Qualls et al., 2014)
Silymarin	(Perez et al., 2014)
TBC	(Lo et al., 2008)
Thymoquinone (TQ)	(Radad et al.,2005)
VIP	(Offen et al., 2000)
Yi-Gan San	(Doo et al., 2010a)
Zinc and Manganese	(Keller et al., 2005)

Figure Legend

Figure 1. Hormetic dose response therapeutic treatment for Parkinson's disease in experimental models. ✹ = mechanism.

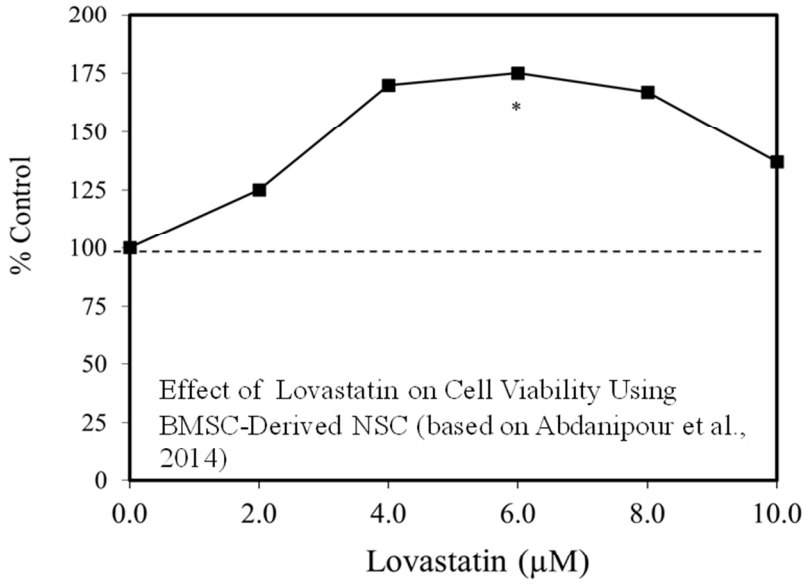

Figure 1. Hormetic dose response therapeutic treatment for Parkinson's disease in experimental models. * = mechanism.
Figure 1A. Abdanipour et al 2014.

254x190mm (96 x 96 DPI)

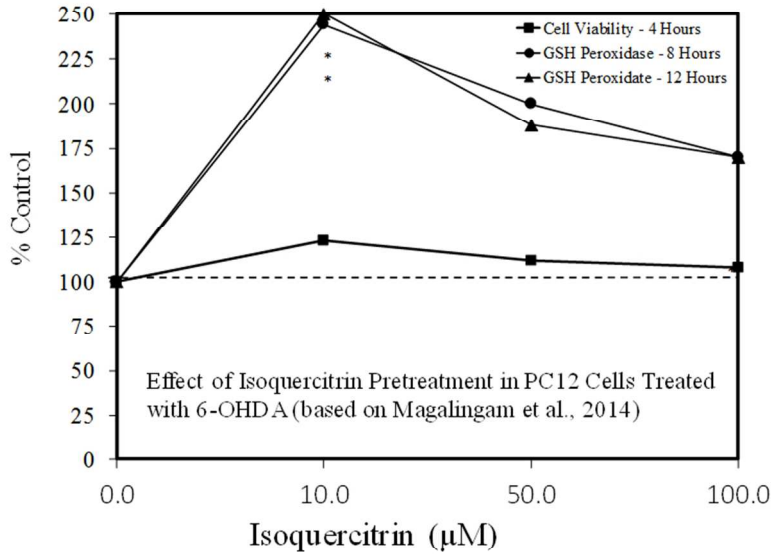

Figure 1AA. Magalingam et al 2014.

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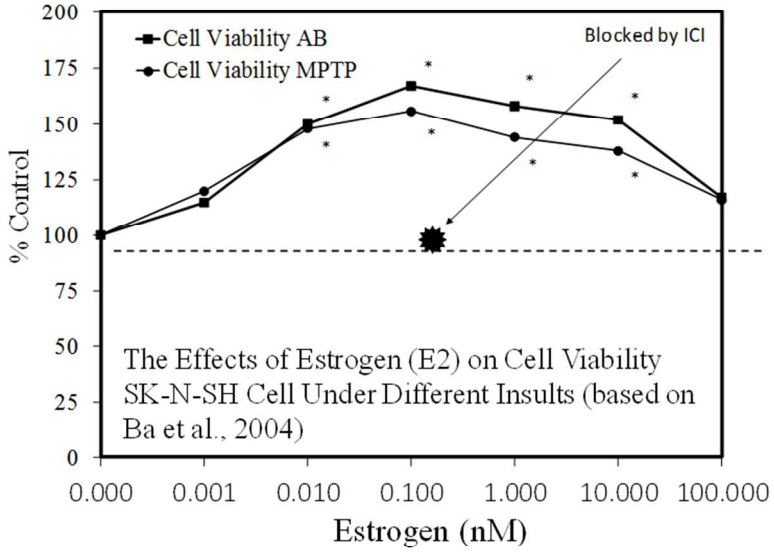

Figure 1 B. Ba et al 2004

254x190mm (96 x 96 DPI)

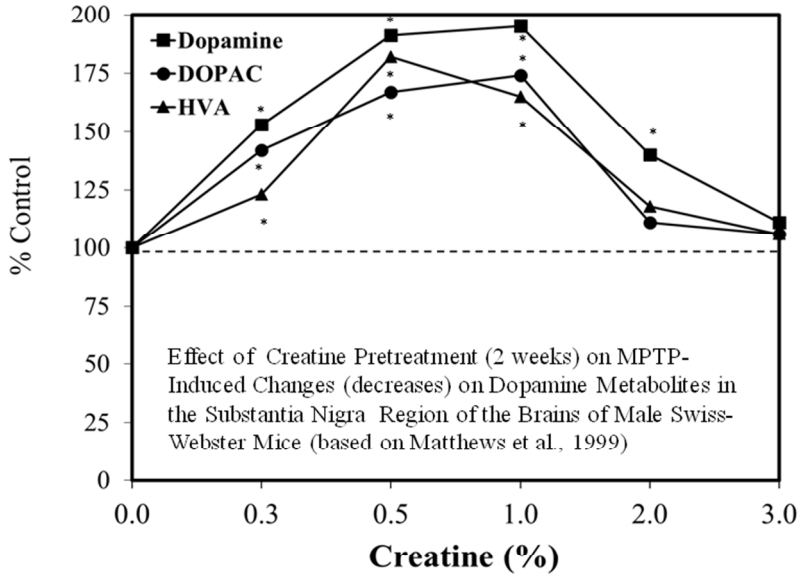

Figure 1BB. Matthews et al 1999.

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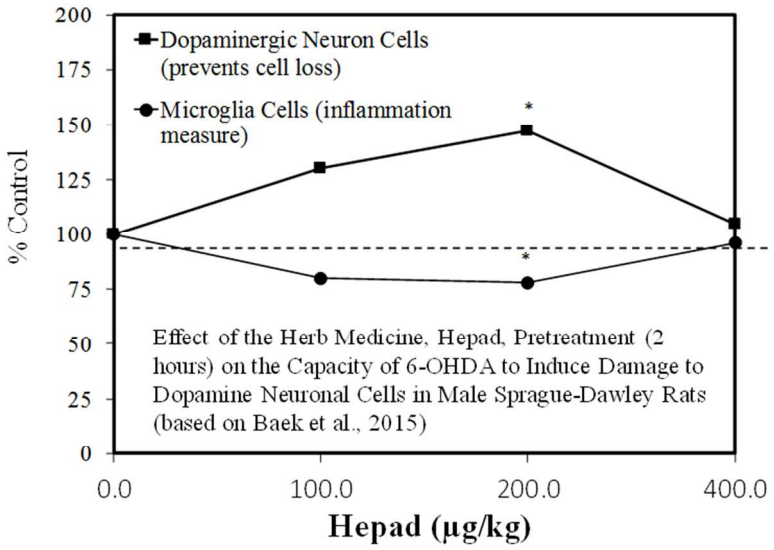

Figure 1 C. Baek et al 2015.

254x190mm (96 x 96 DPI)

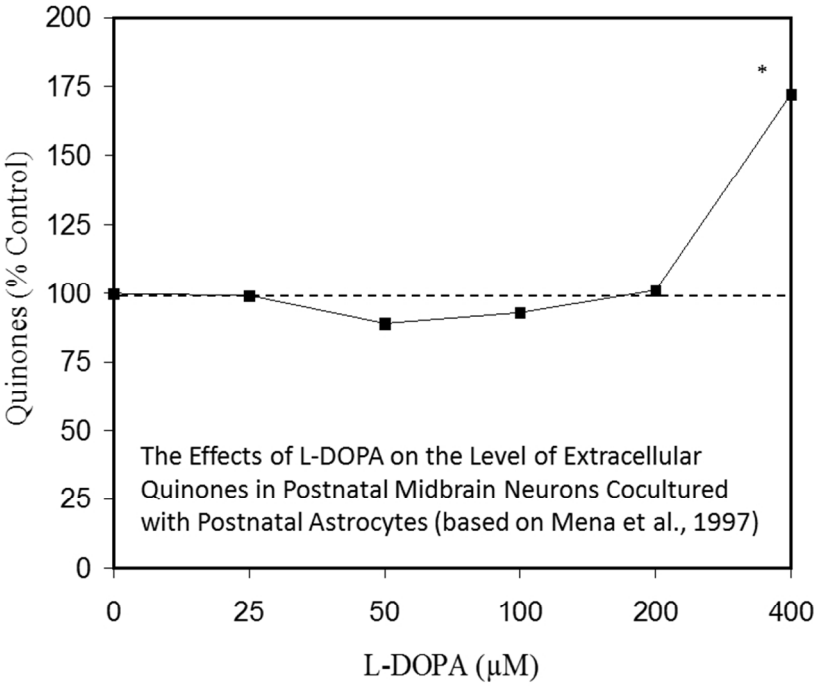

Figure 1 CC. Mena et al 1997.

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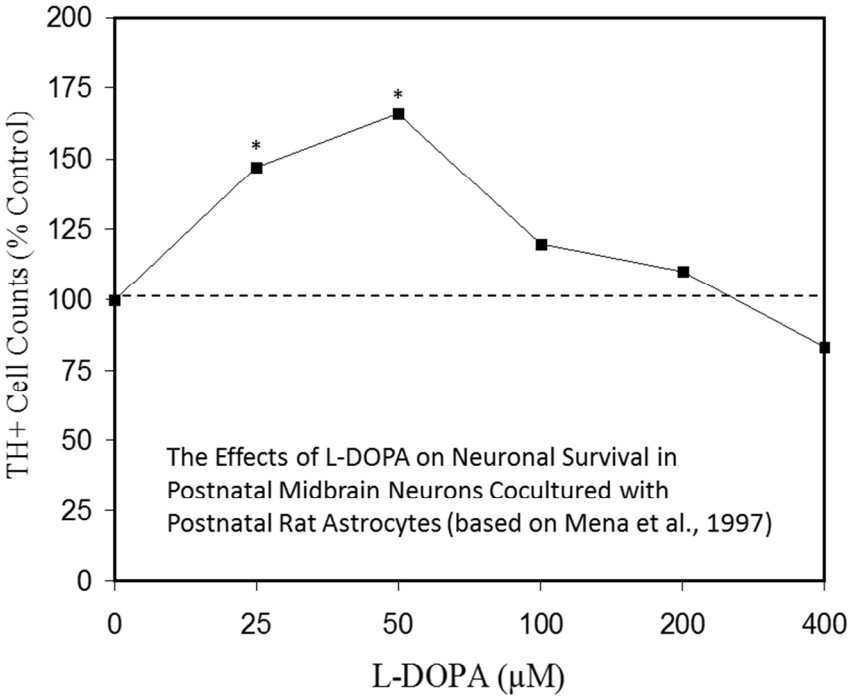

Figure 1 CC continued. Mena et al 1997

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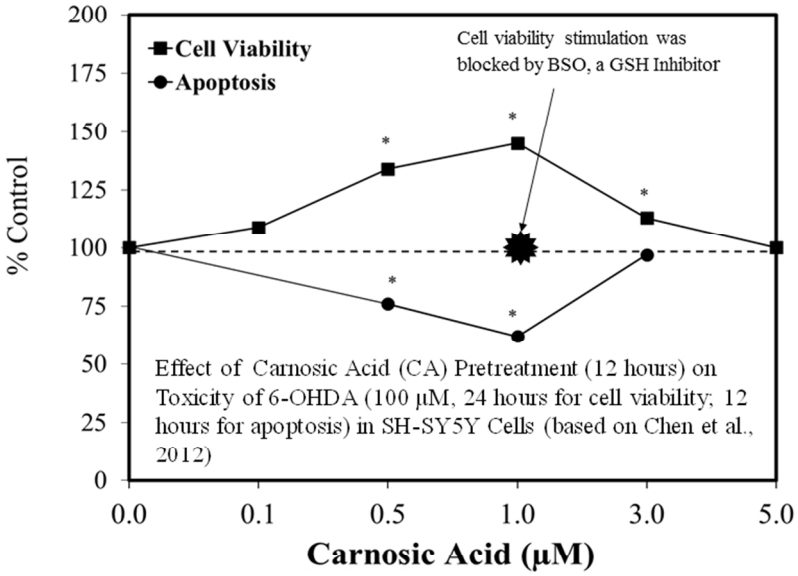

Figure 1 D. Chen et al 2012.

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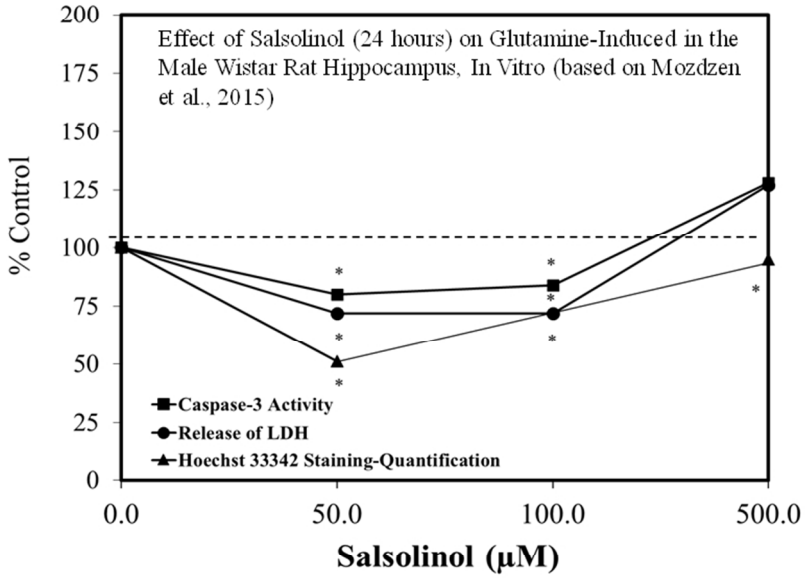

Figure 1 DD. Mozdzen et al 2015.

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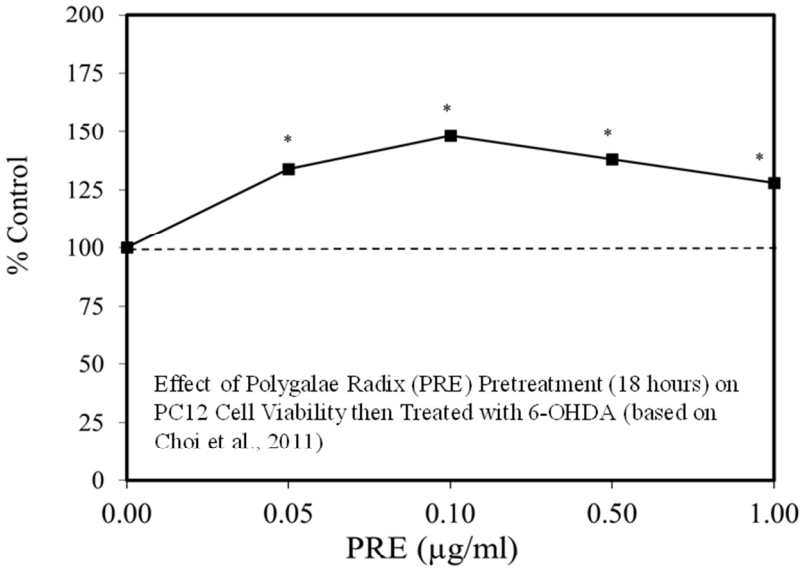

Figure 1 E. Choi et al 2011.

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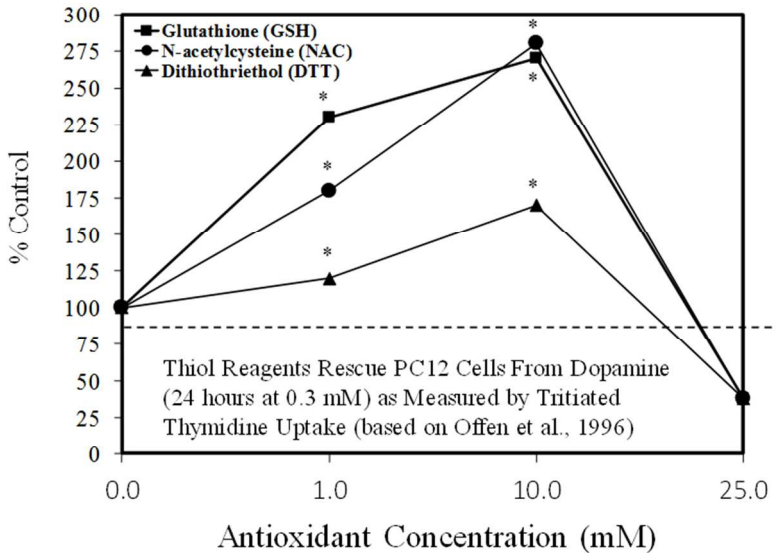

Figure 1 EE. Offen et al 1996.

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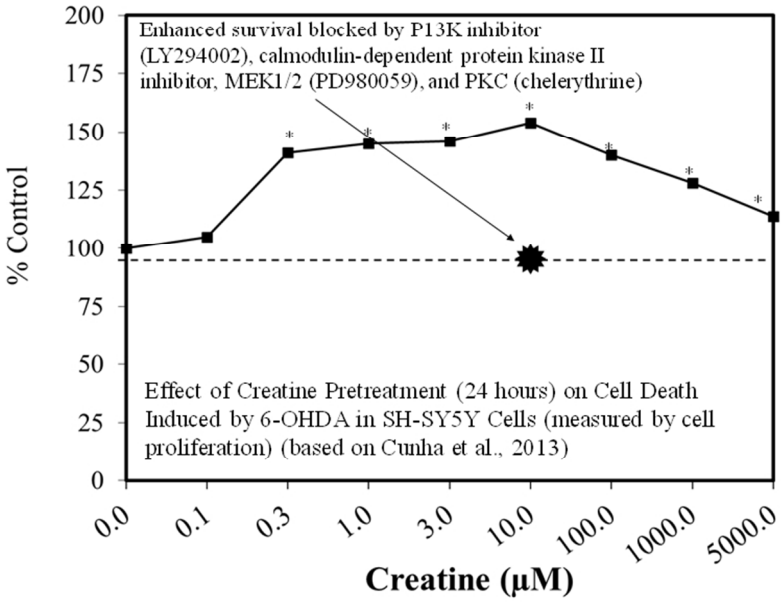

Figure 1 D. Cunha et al 2013.

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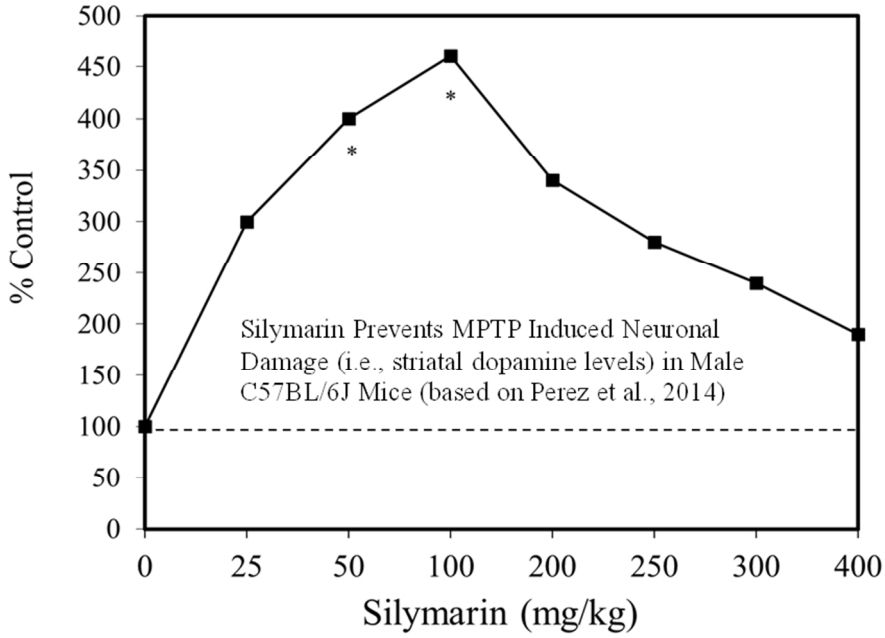

Figure 1 FF. Perez-H et al 2014.

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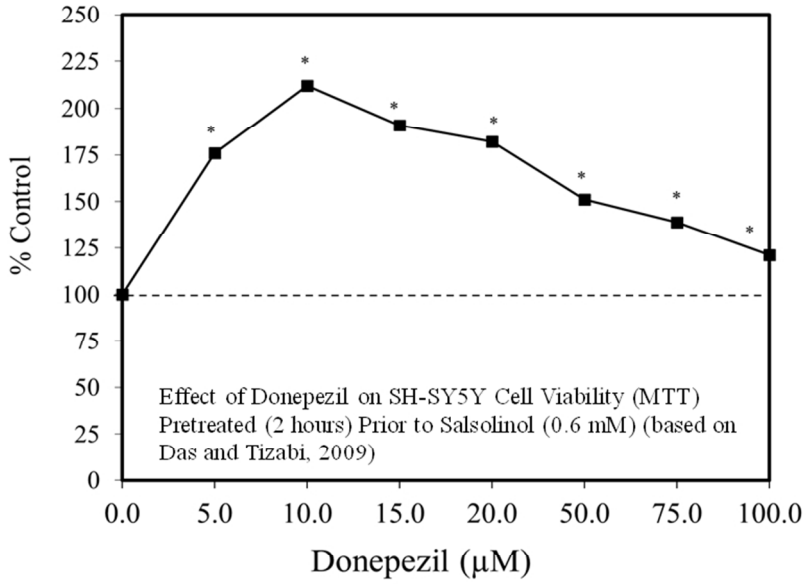

Figure 1 G. Das and Tizabi 2009.

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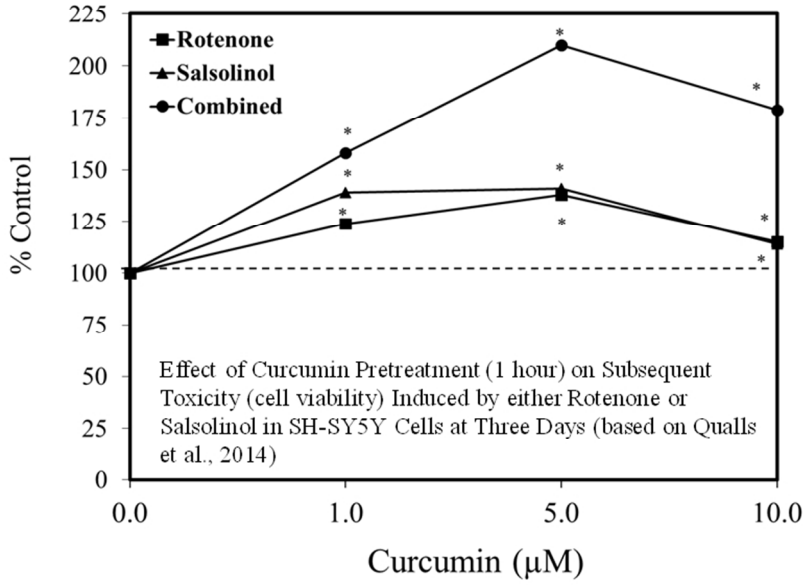

Figure 1 GG. Qualls et al 2014.

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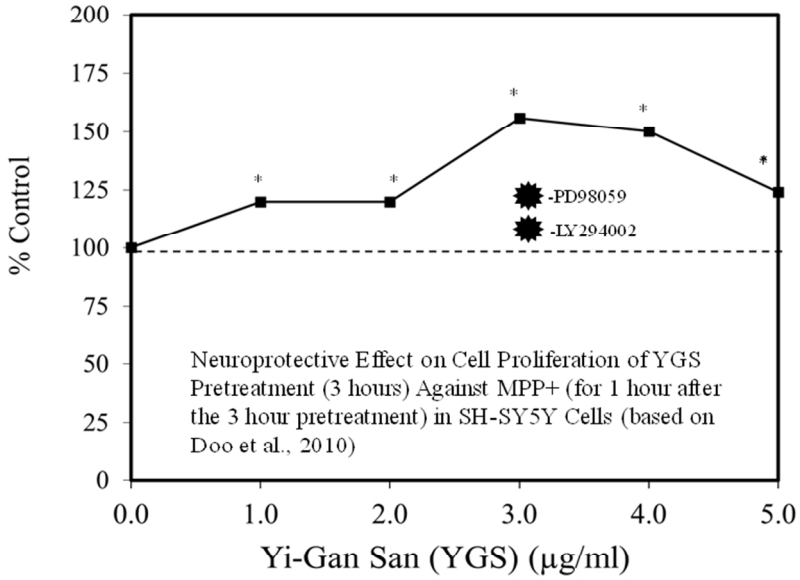

Figure 1 H. Doo et al 2010.

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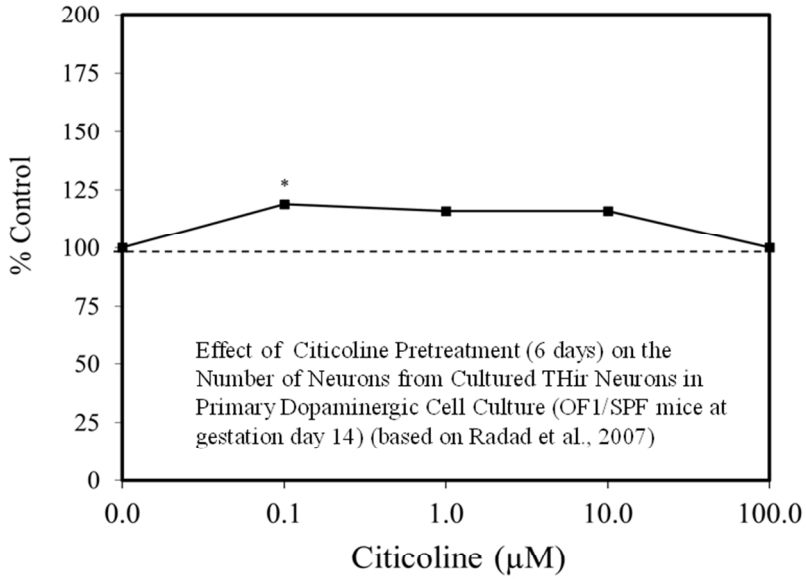

Figure 1 HH. Radad et al 2007.

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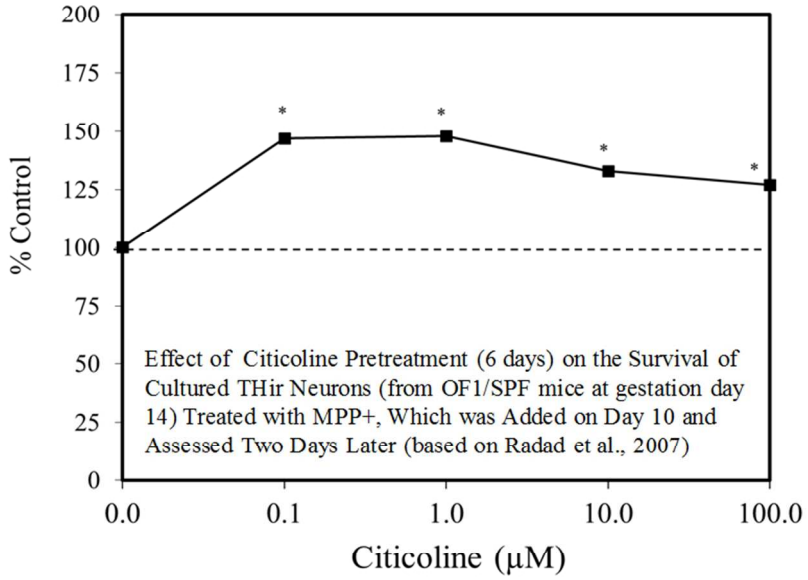

Figure 1 HH continued. Radad et al 2017.

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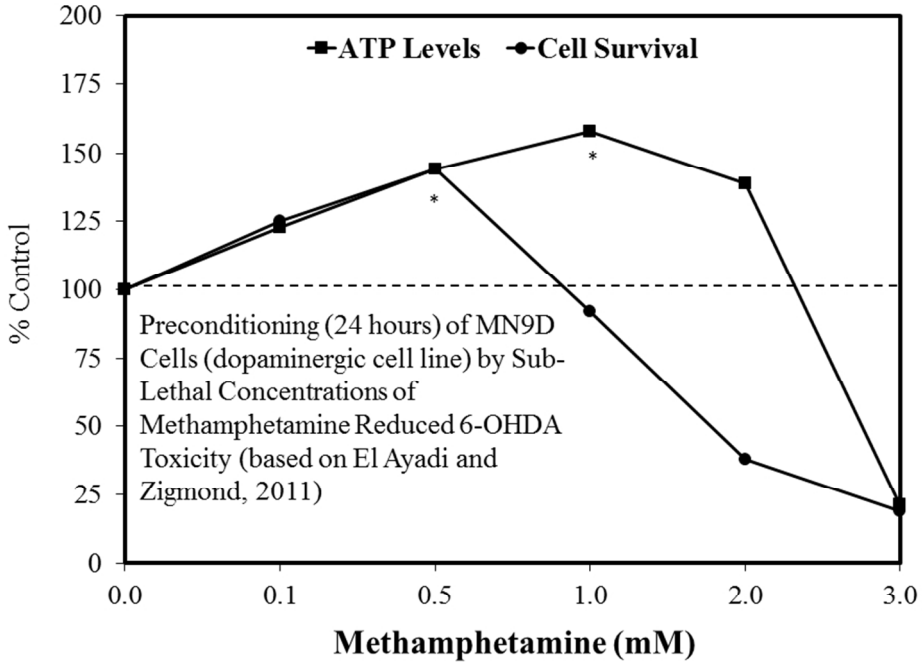

Figure 1 I. El Ayadi and Zigmond 2001.

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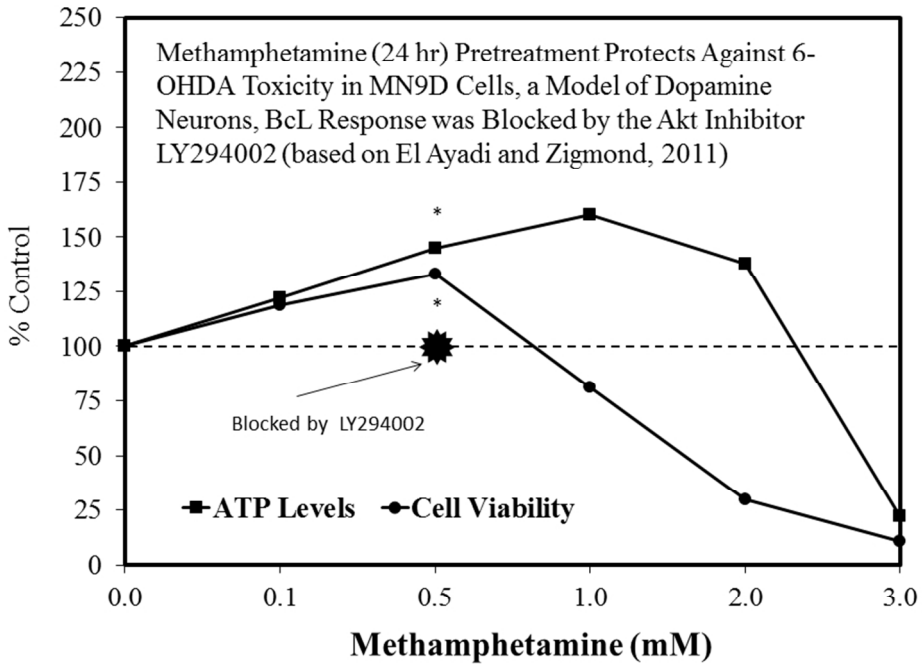

Figure 1 I continued. El Ayadi and Zigmond 2001.

254x190mm (96 x 96 DPI)

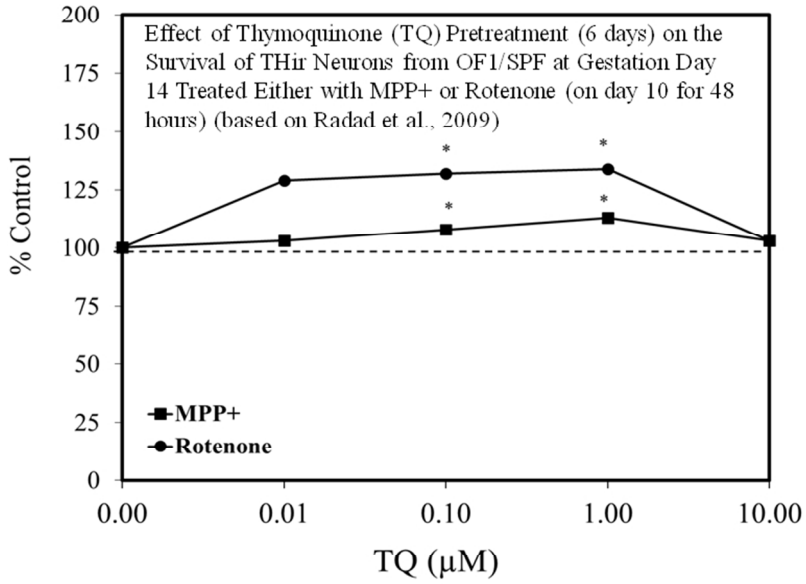

Figure 1 II. Radad et al 2009.

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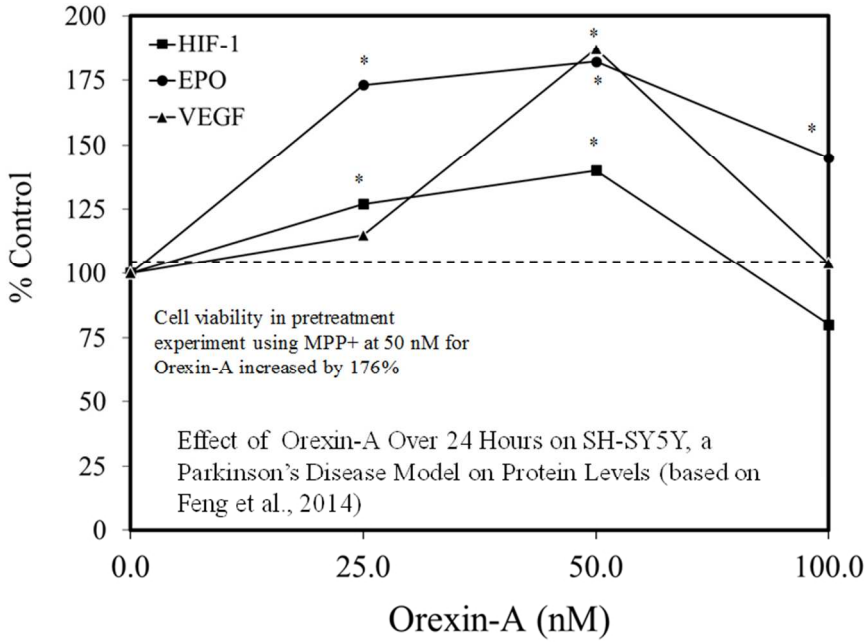

Figure 1J. Feng et al 2014.

254x190mm (96 x 96 DPI)

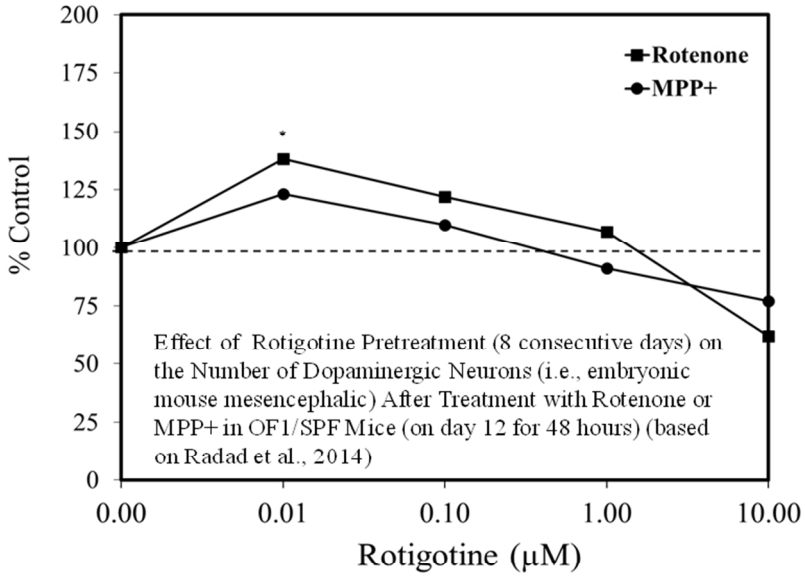

Figure 1 JJ. Radad et al 2014.

254x190mm (96 x 96 DPI)

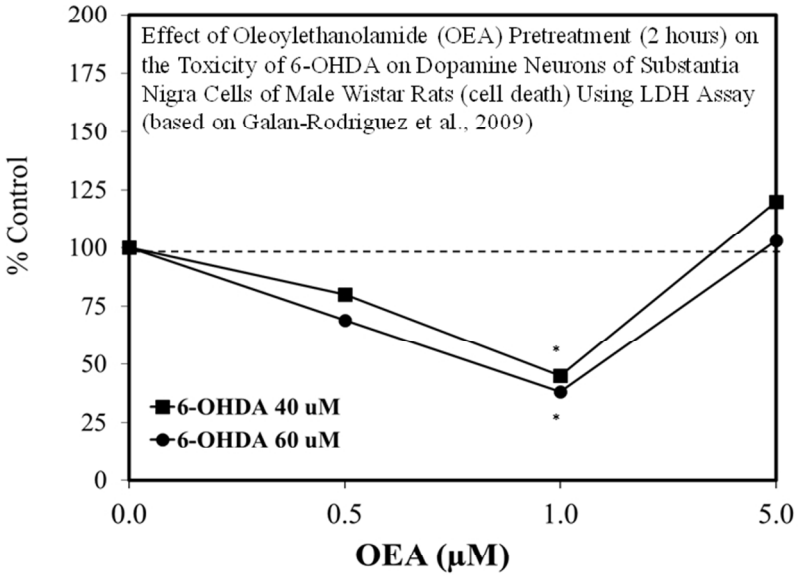

Figure 1 K. Galan-Rodriguez et al 2009.

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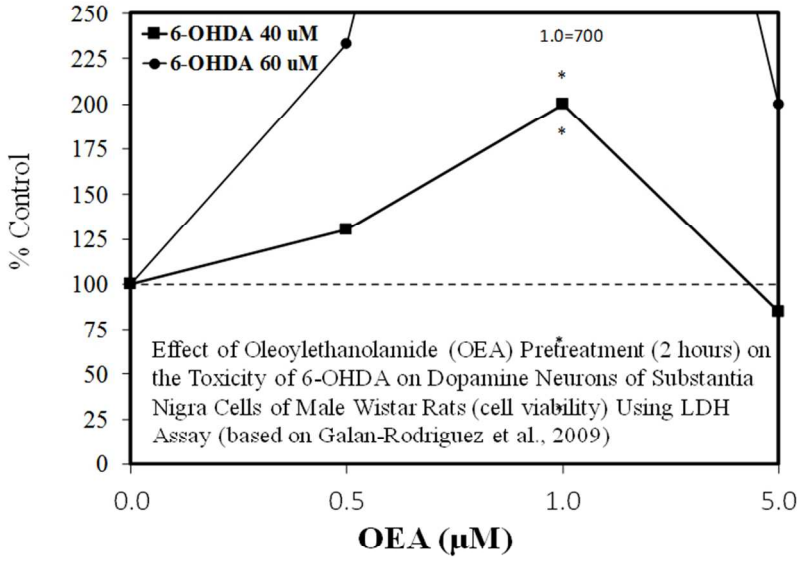

Figure 1 K continued. Galan-Rodriguez et al 2009

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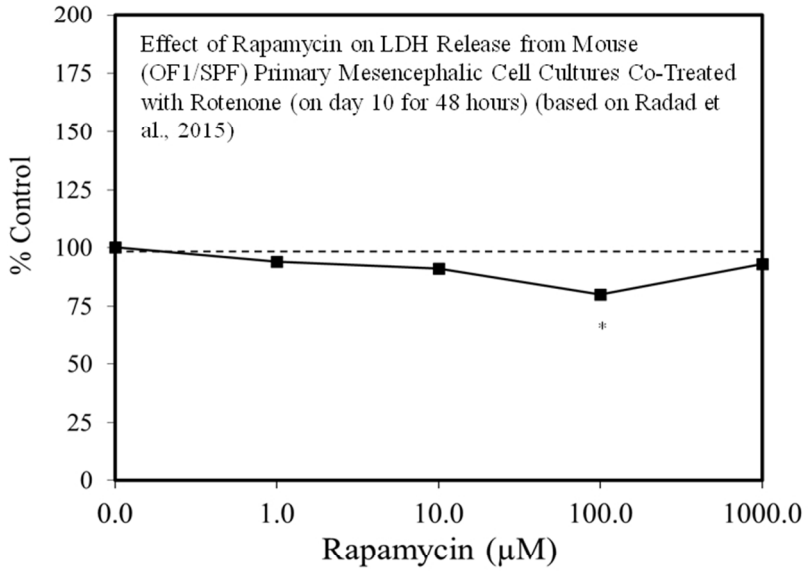

Figure 1 KK. Radad et al 2015.

254x190mm (96 x 96 DPI)

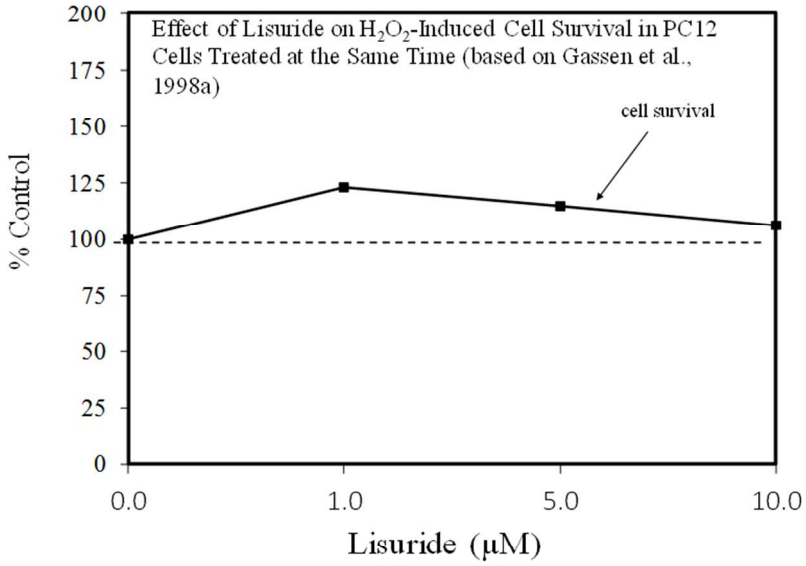

Figure 1 L. Gassen et al 1998a.

254x190mm (96 x 96 DPI)

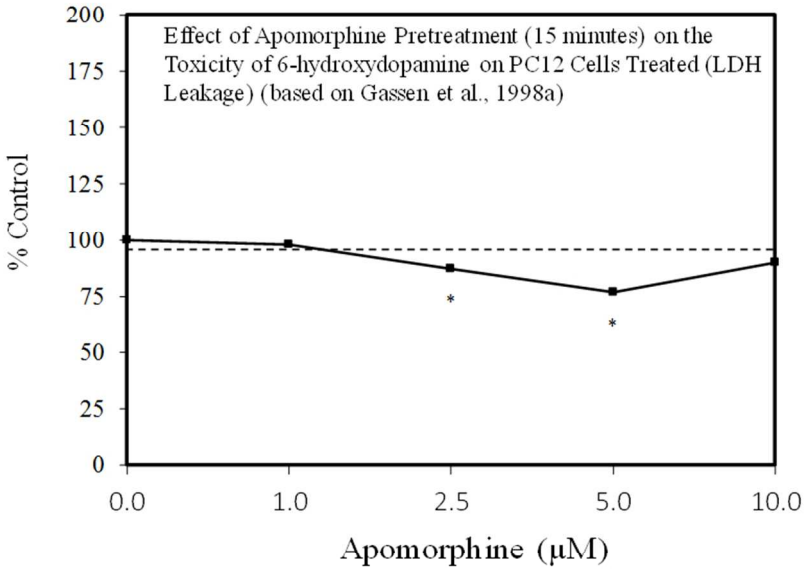

Figure 1 L continued Gassen et al 1998a.

254x190mm (96 x 96 DPI)

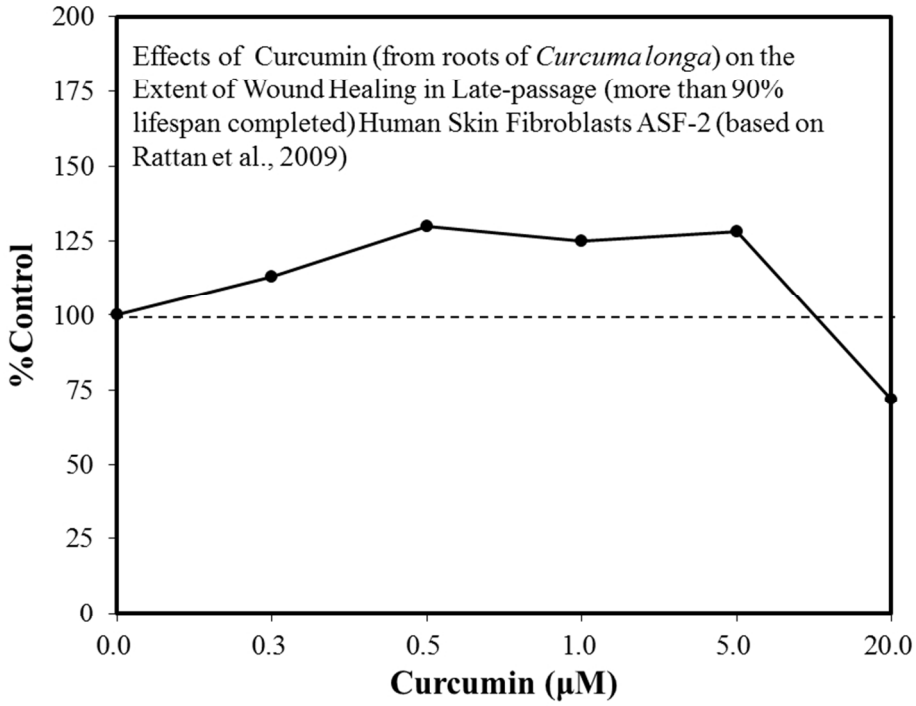

Figure 1 LL. Rattan et al 2009.

254x190mm (96 x 96 DPI)

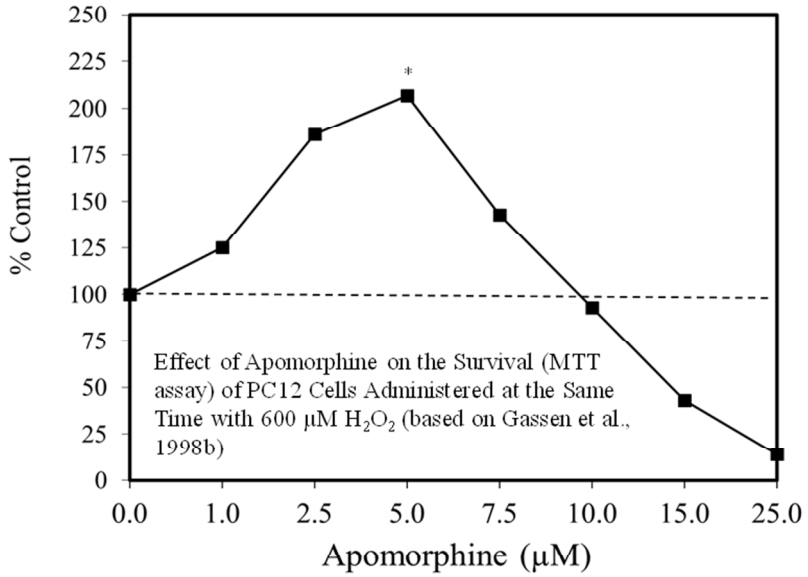

Figure 1 M. Gassen et al 1998b.

254x190mm (96 x 96 DPI)

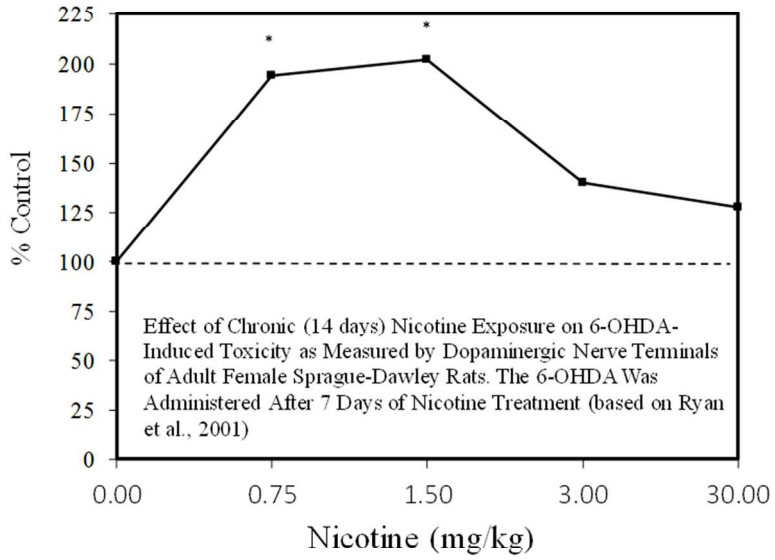

Figure 1 MM. Ryan et al 2001.

254x190mm (96 x 96 DPI)

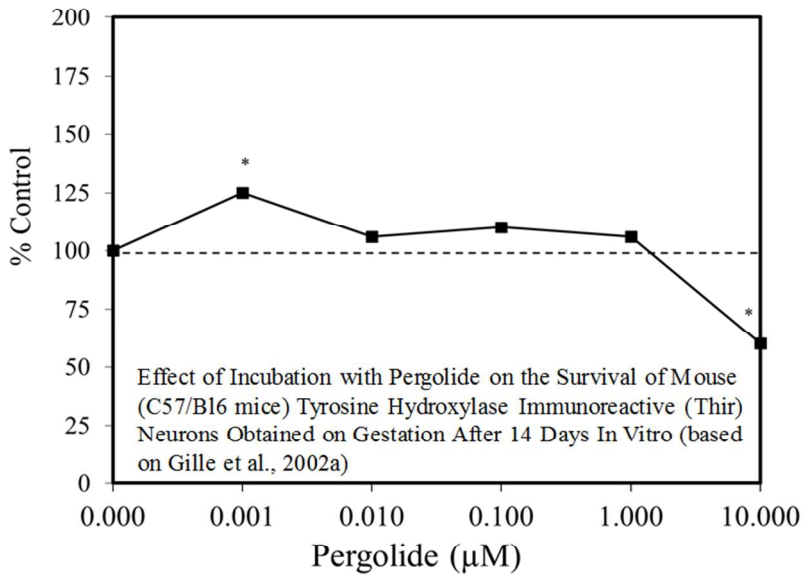

Figure 1 N. Gille et al 2002a.

254x190mm (96 x 96 DPI)

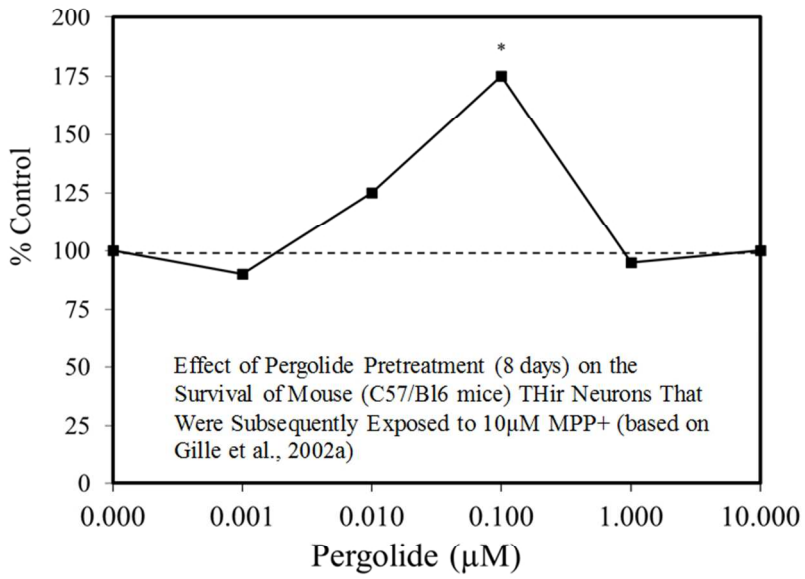

Figure 1 N. Gille et al 2002a continued.

254x190mm (96 x 96 DPI)

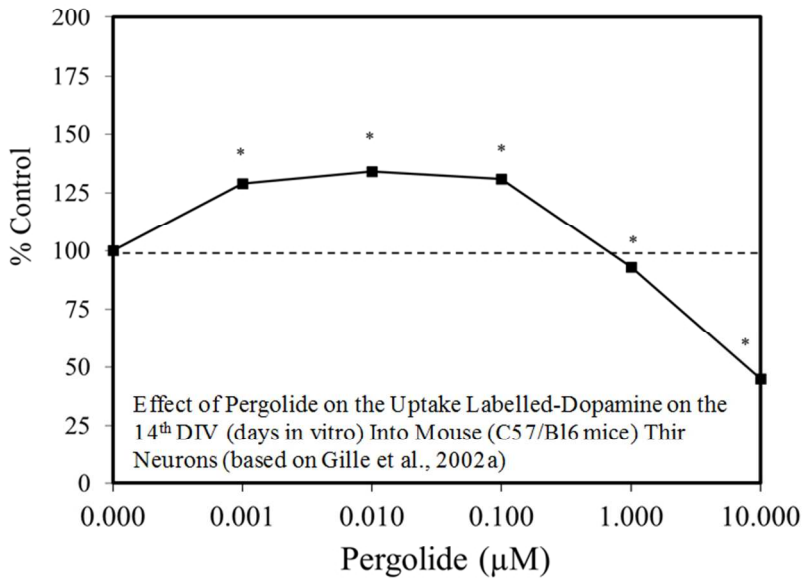

Figure 1 N. Gille et al 2002a continued.

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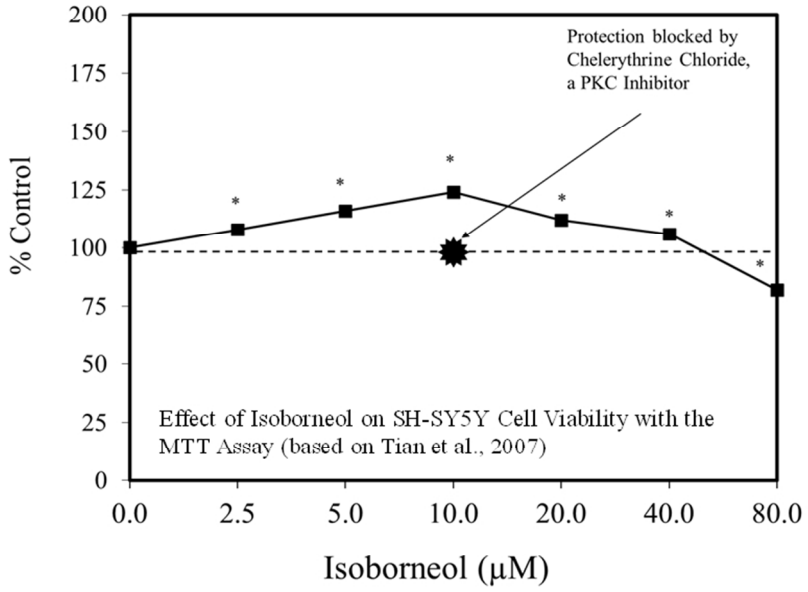

Figure 1 NN. Tian et al 2007.

254x190mm (96 x 96 DPI)

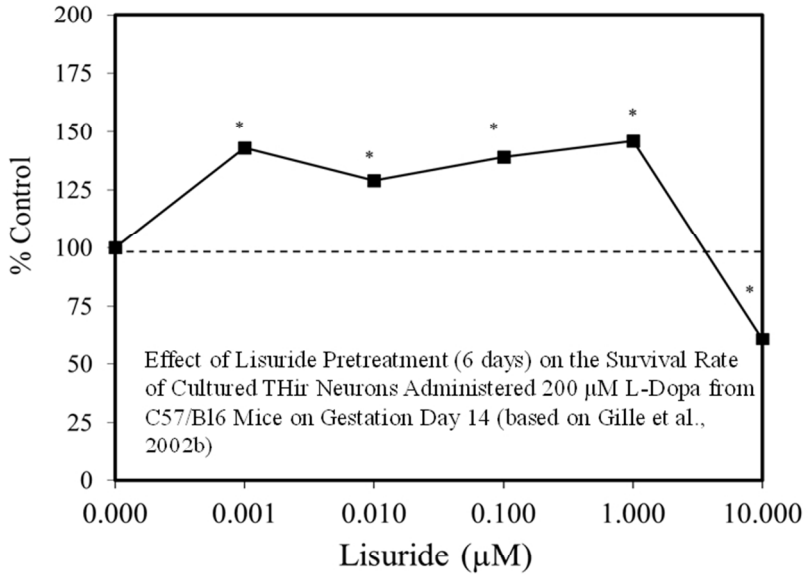

Figure 1 O. Gille et al 2002b.

254x190mm (96 x 96 DPI)

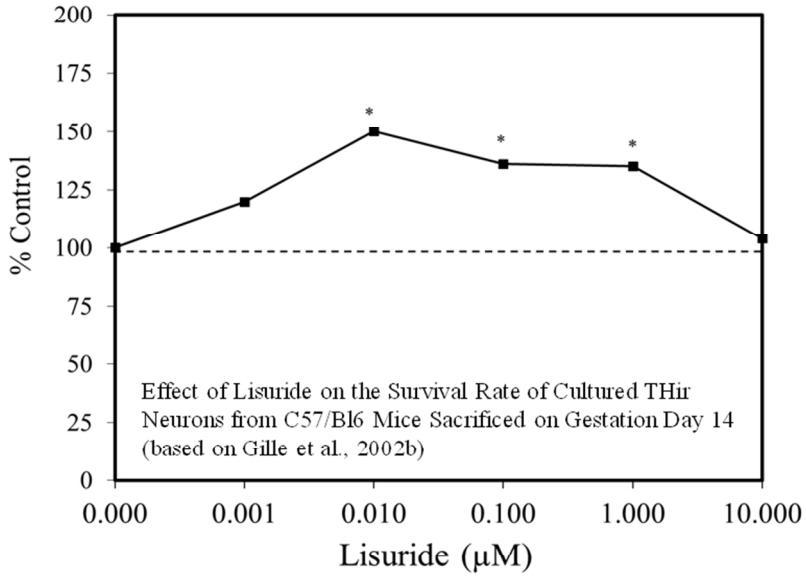

Figure 1 O. Gille et al 2002b continued.

254x190mm (96 x 96 DPI)

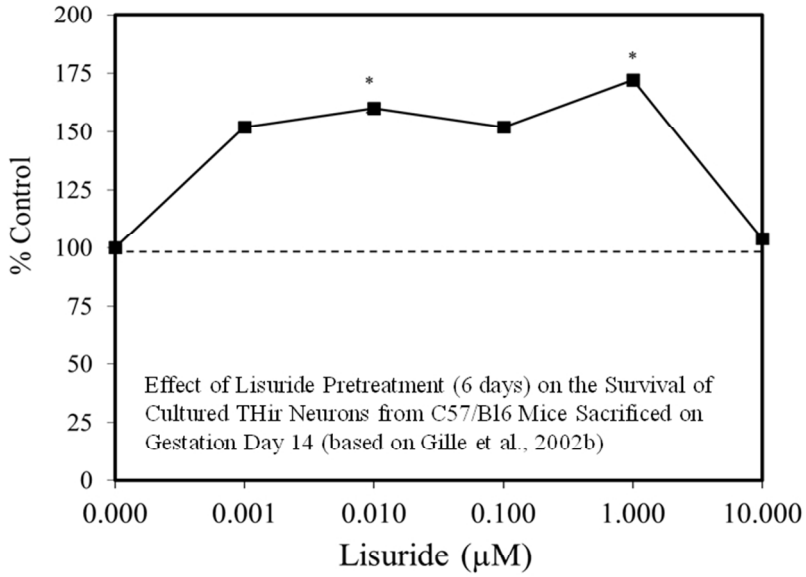

Figure 1 O. Gille et al 2002b continued.

254x190mm (96 x 96 DPI)

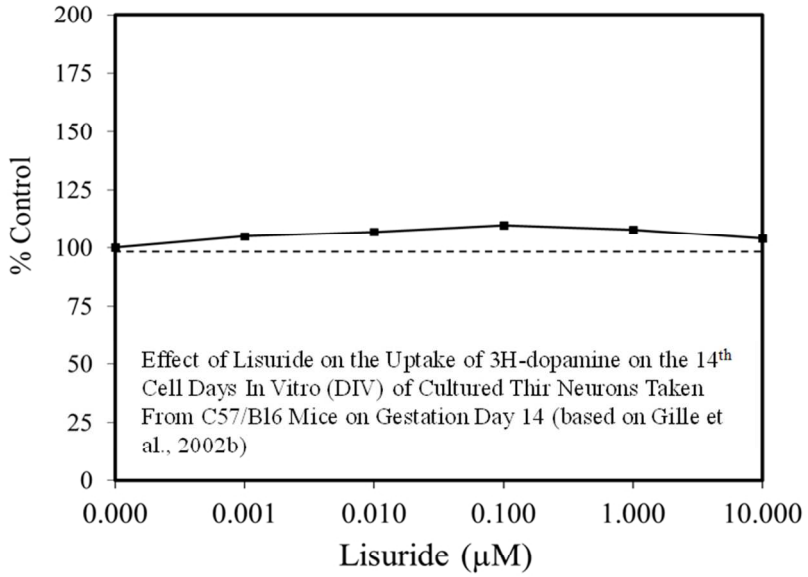

Figure 1 O. Gille et al 2002b continued.

254x190mm (96 x 96 DPI)

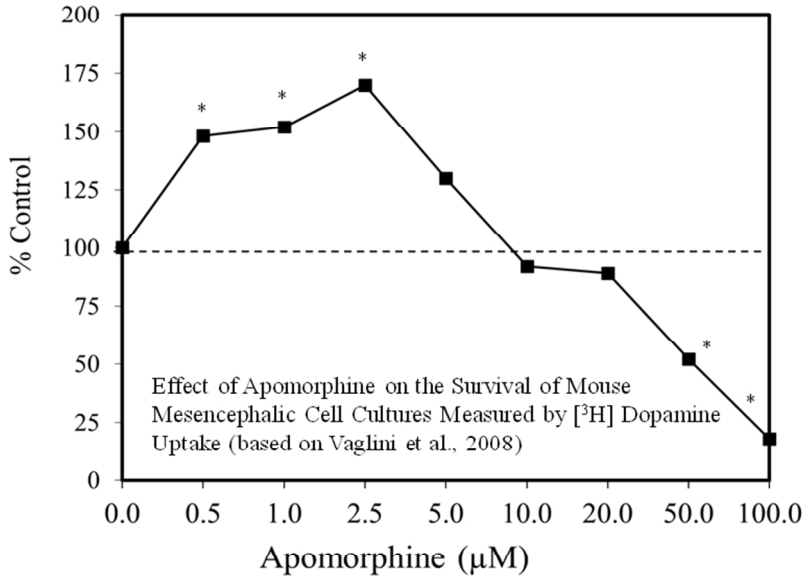

Figure 1 OO. Vaglini et al 2008.

254x190mm (96 x 96 DPI)

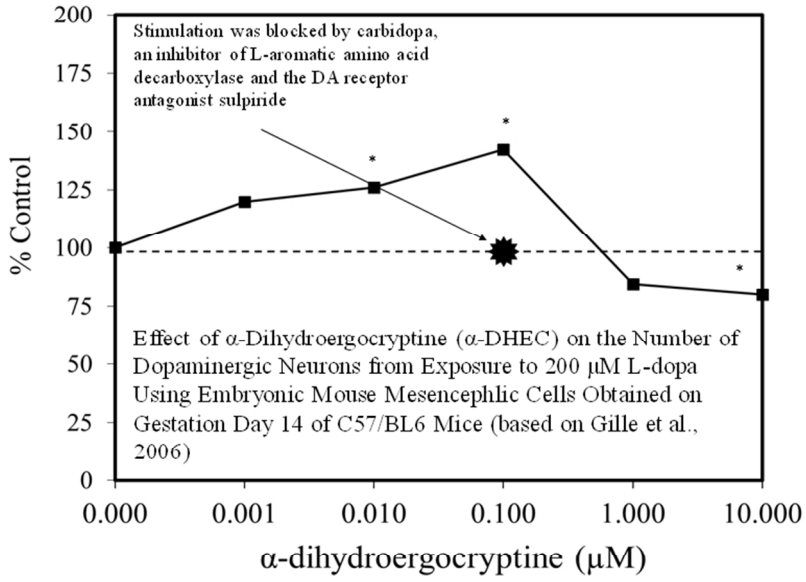

Figure 1 P. Gille et al 2006.

254x190mm (96 x 96 DPI)

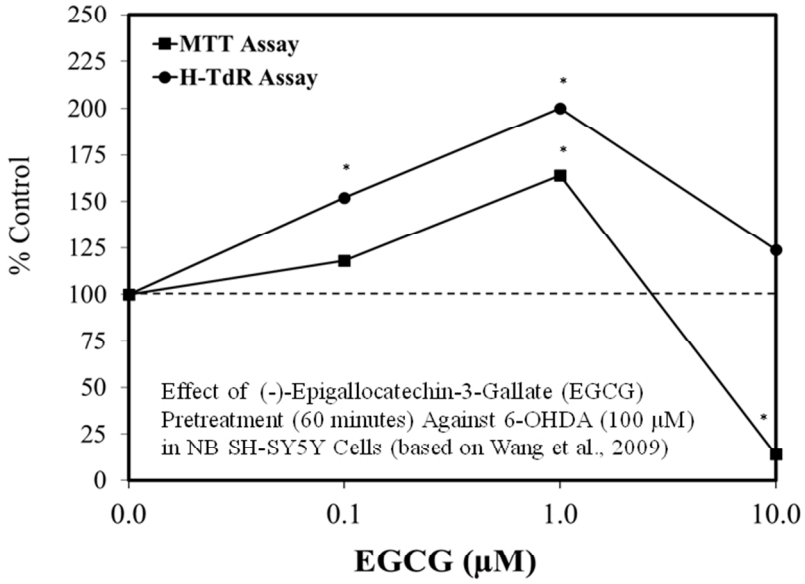

Figure 1 PP. Wang et al 2009.

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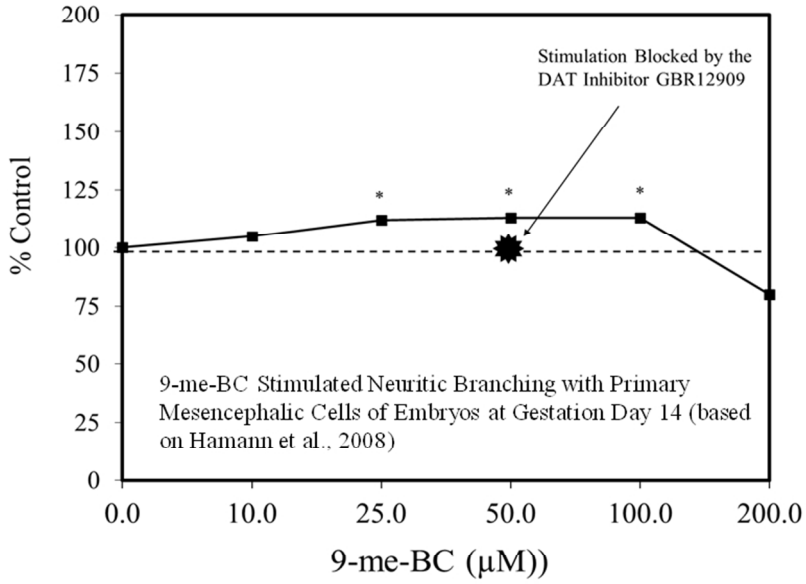

Figure 1 Q. Hamann et al 2008.

254x190mm (96 x 96 DPI)

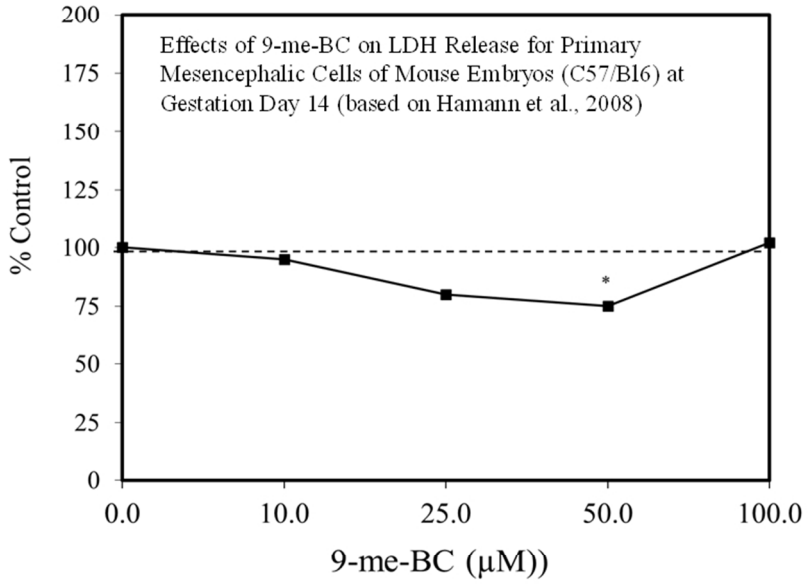

Figure 1 Q continued. Hamann et al 2008.

254x190mm (96 x 96 DPI)

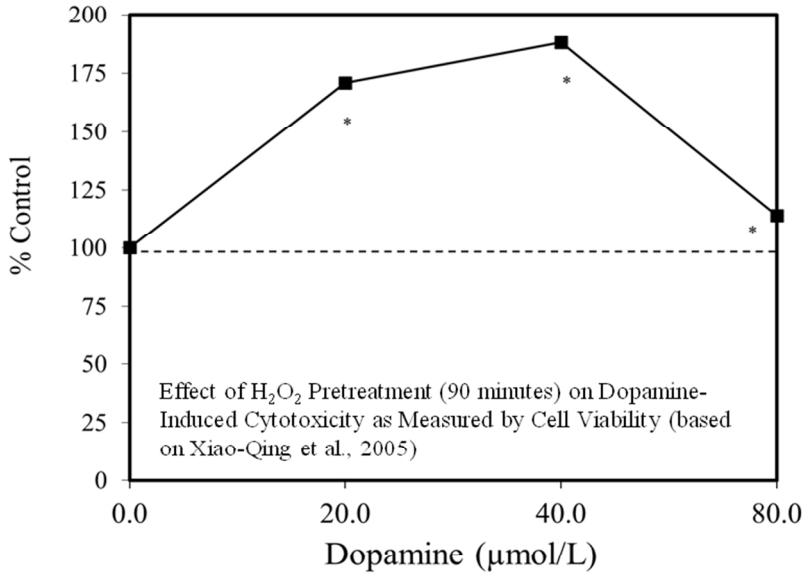

Figure 1 QQ. Xiao-Quing et al 2005.

254x190mm (96 x 96 DPI)

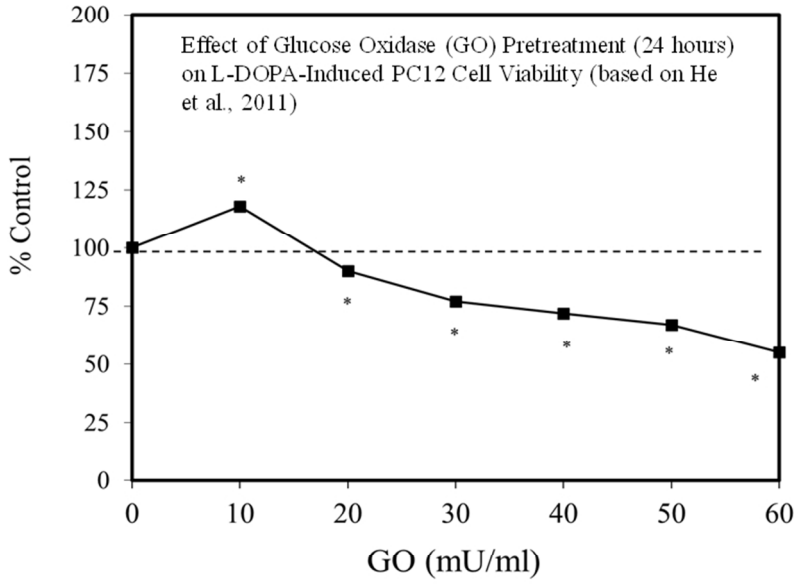

Figure 1 R. He et al 2011.

254x190mm (96 x 96 DPI)

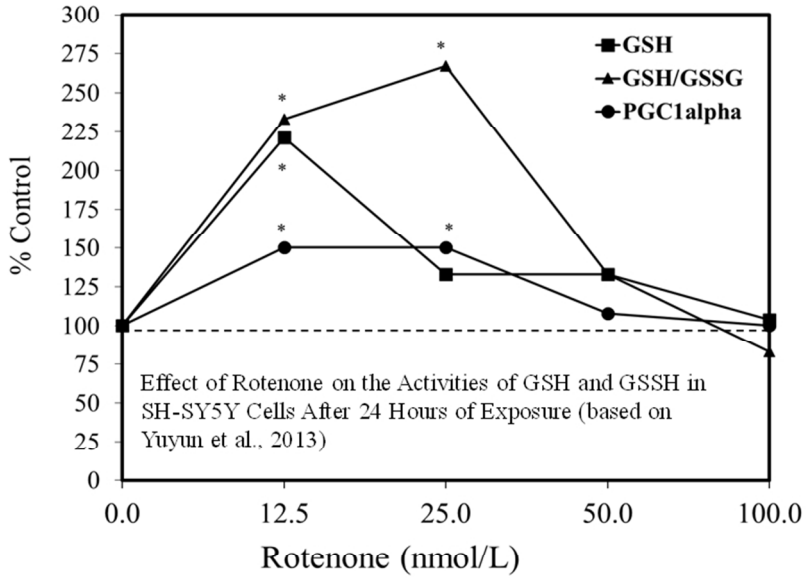

Figure 1 RR. Yuyun et al 2013.

254x190mm (96 x 96 DPI)

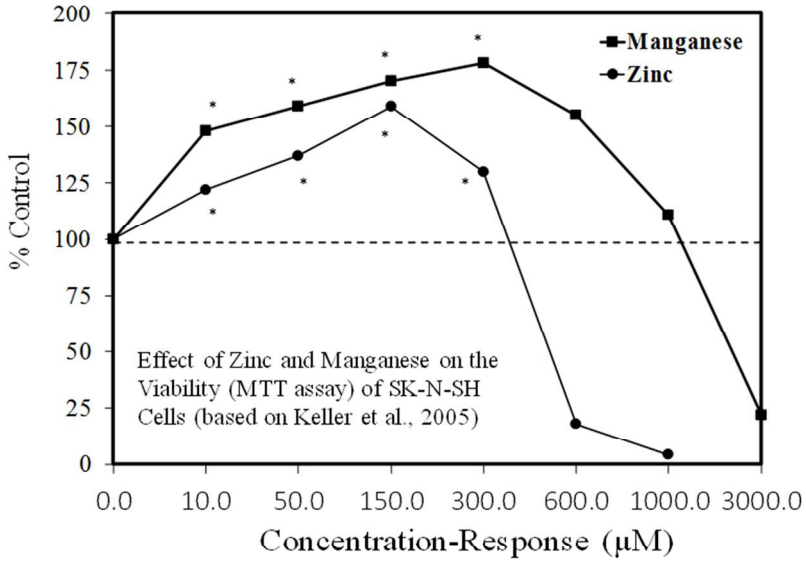

Figure 1 S. Keller et al 2005.

254x190mm (96 x 96 DPI)

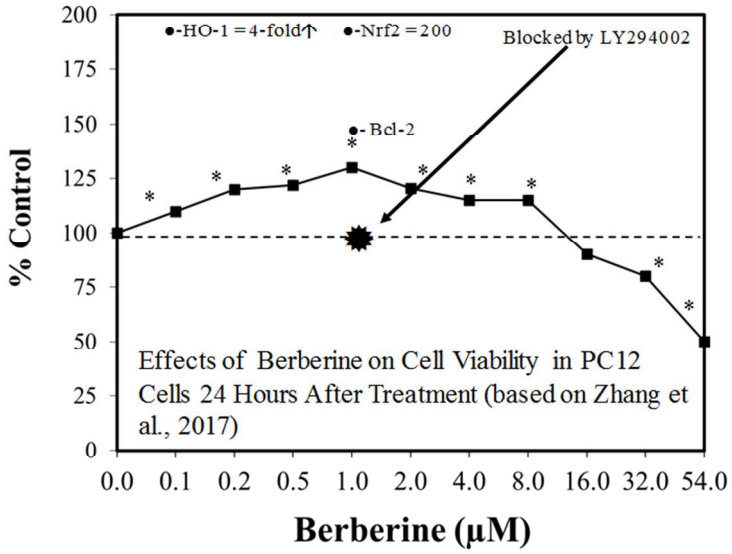

Figure 1 SS. Zhang et al 20017a.

254x190mm (96 x 96 DPI)

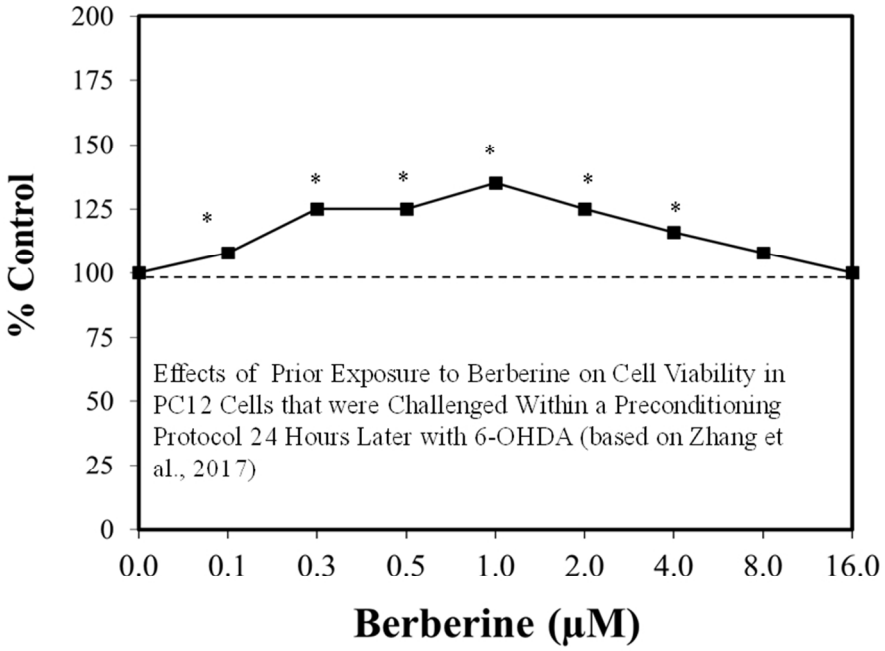

Figure 1 SS continued. Zhang et al 2017a.

254x190mm (96 x 96 DPI)

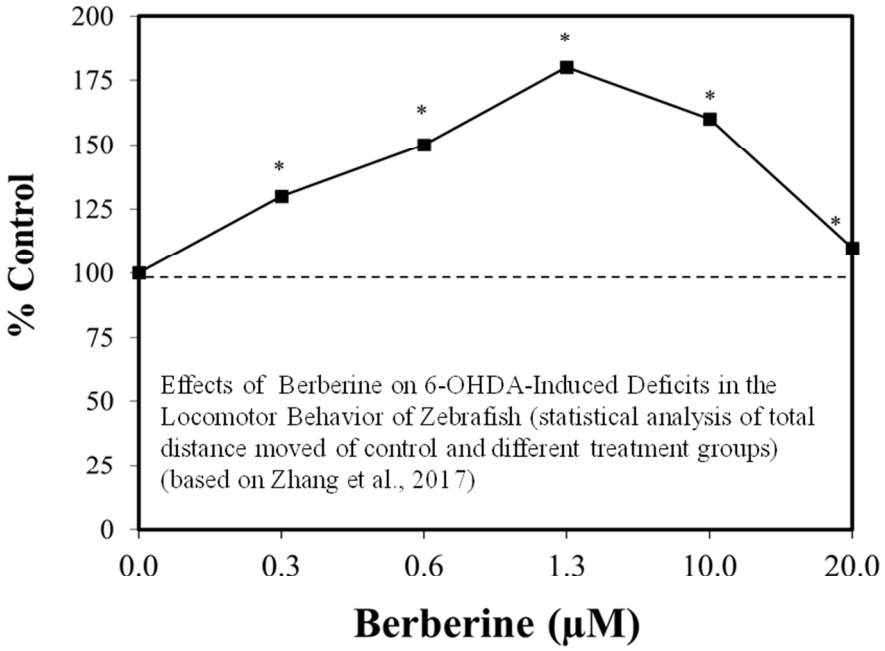

Figure 1 SS continued. Zhang et al 2017a.

254x190mm (96 x 96 DPI)

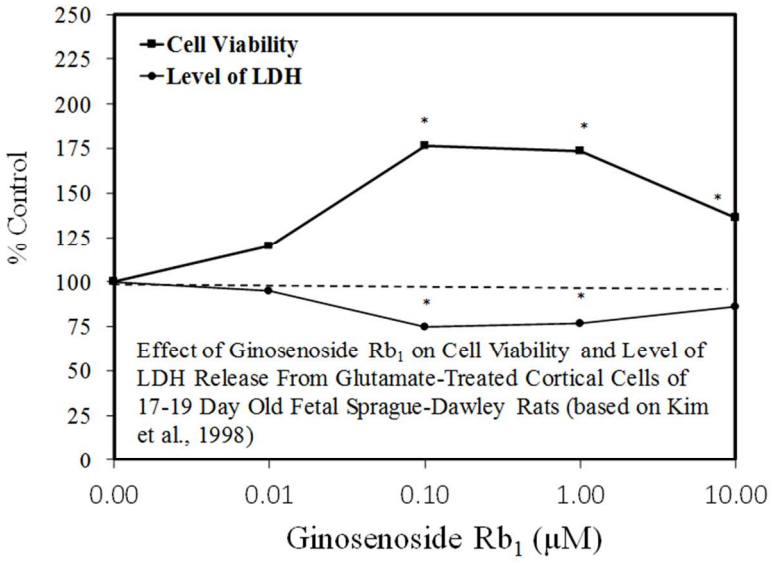

Figure 1 T Kim et al 1998.

254x190mm (96 x 96 DPI)

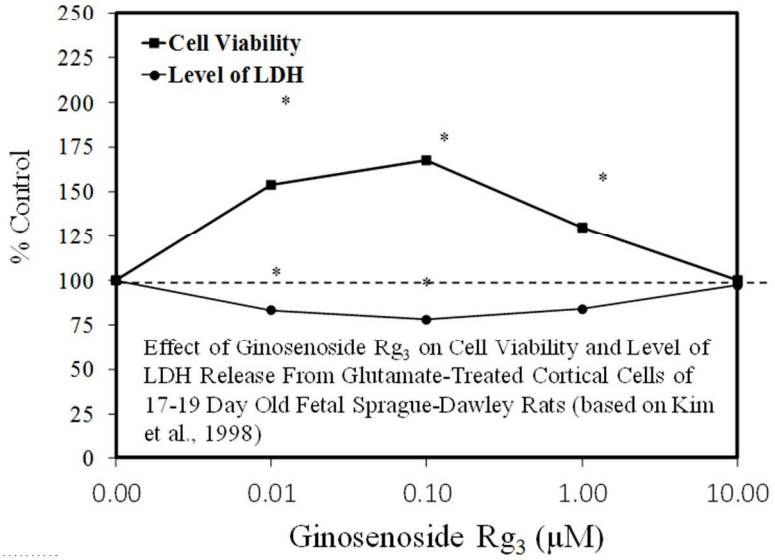

Figure 1 T continued. Kim et al 1998.

254x190mm (96 x 96 DPI)

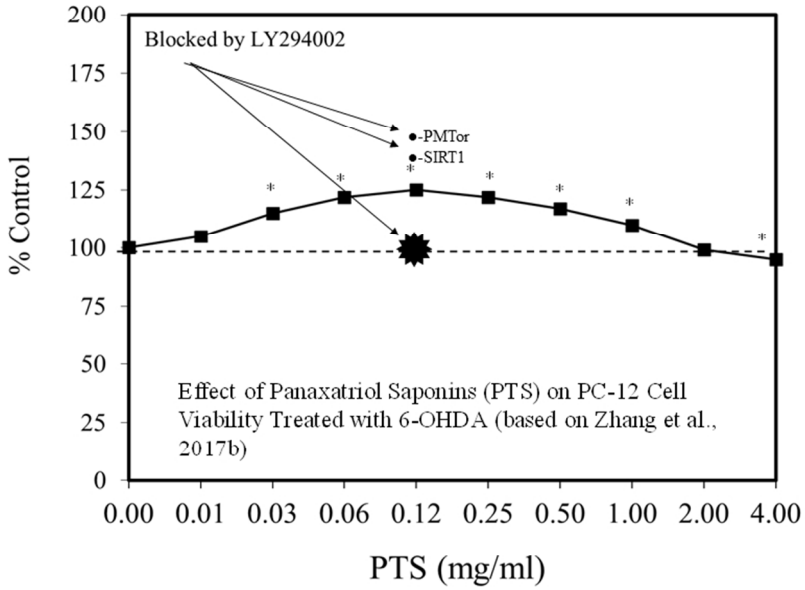

Figure 1 TT. Zhang et al 2017b.

254x190mm (96 x 96 DPI)

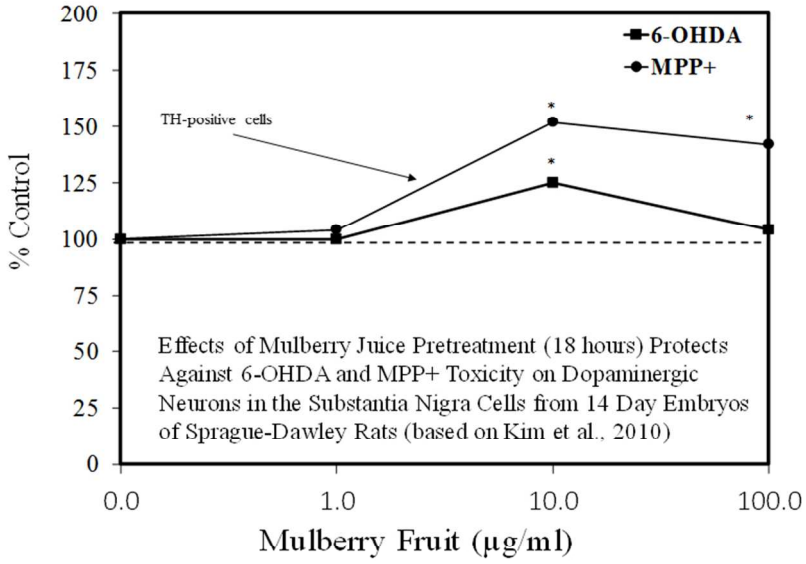

Figure 1 U. Kim et al 2010.

254x190mm (96 x 96 DPI)

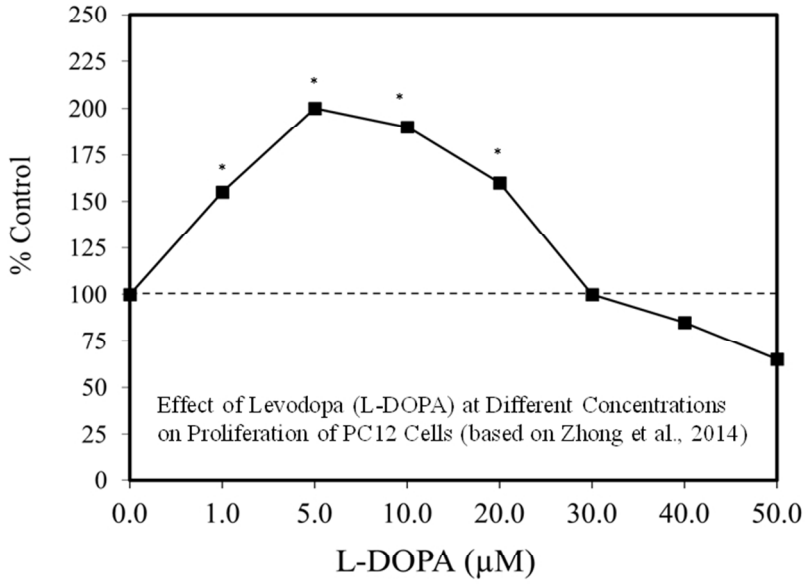

Figure 1 UU. Zhong et al 2014.

254x190mm (96 x 96 DPI)

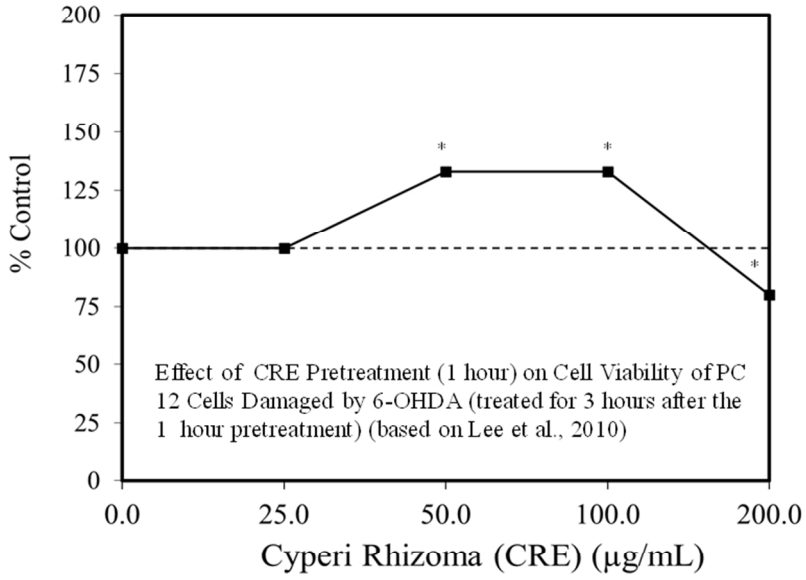

Figure 1 V. Lee et al 2010.

254x190mm (96 x 96 DPI)

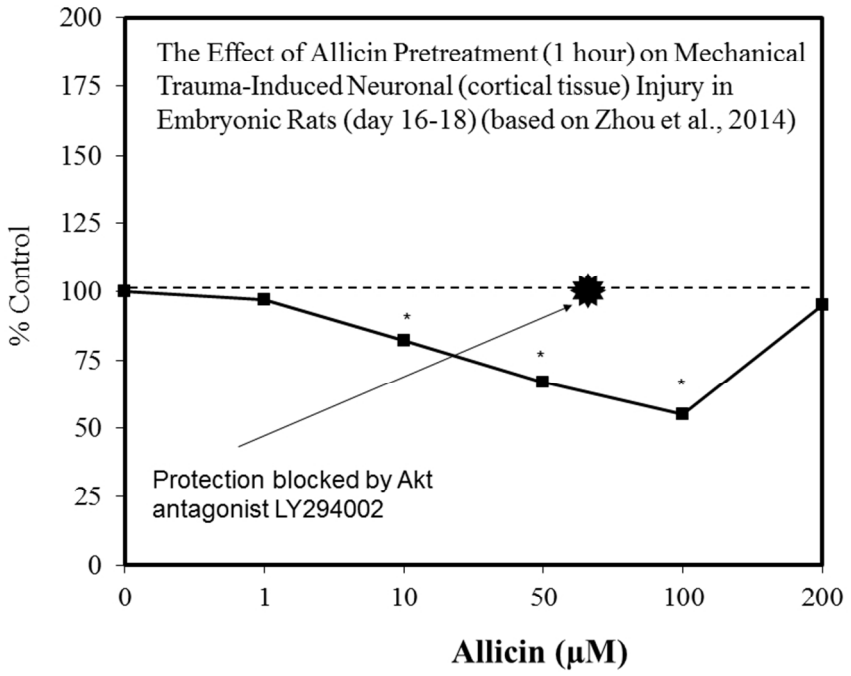

Figure 1 VV. Zhou et al 2014.

254x190mm (96 x 96 DPI)

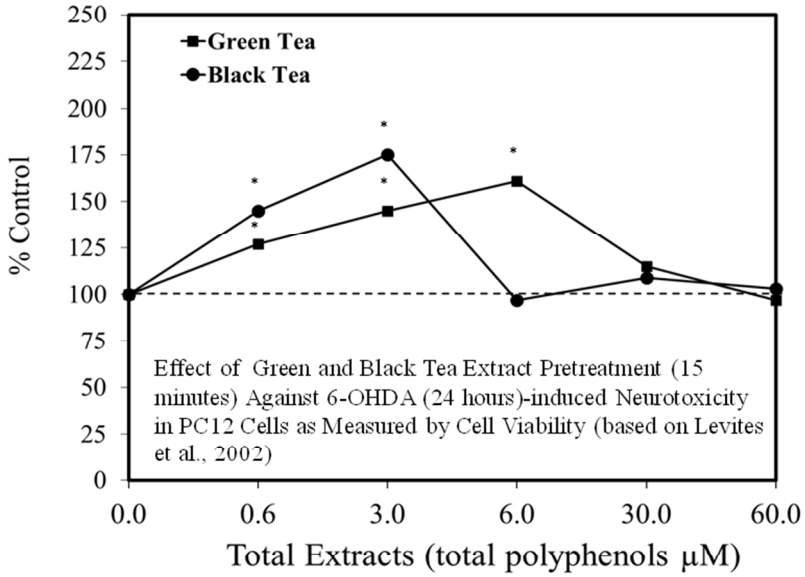

Figure 1 W. Levites et al 2002.

254x190mm (96 x 96 DPI)

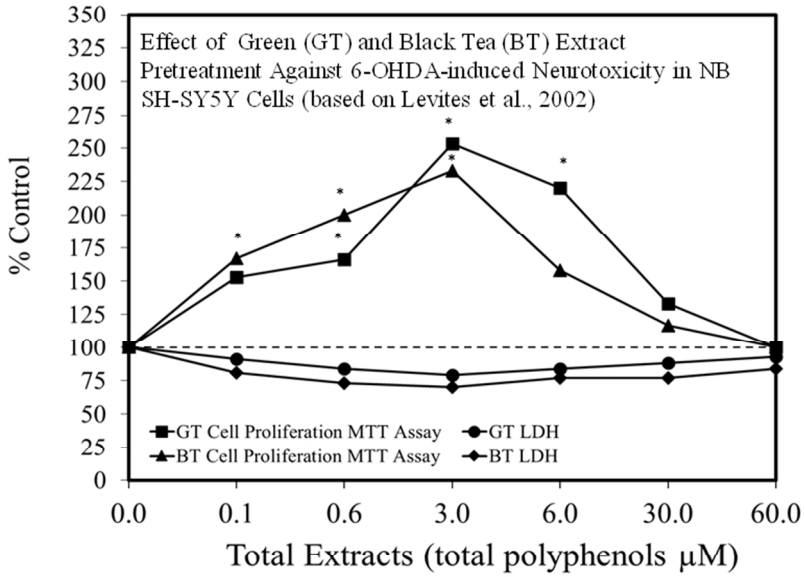

Figure 1 W continued. Levites et al 2002.

254x190mm (96 x 96 DPI)

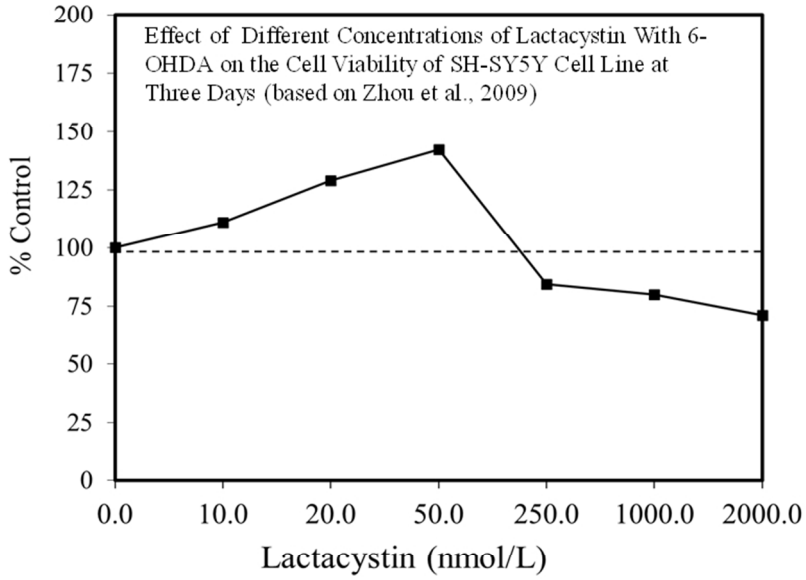

Figure 1 WW. Zhou et al 2009..

254x190mm (96 x 96 DPI)

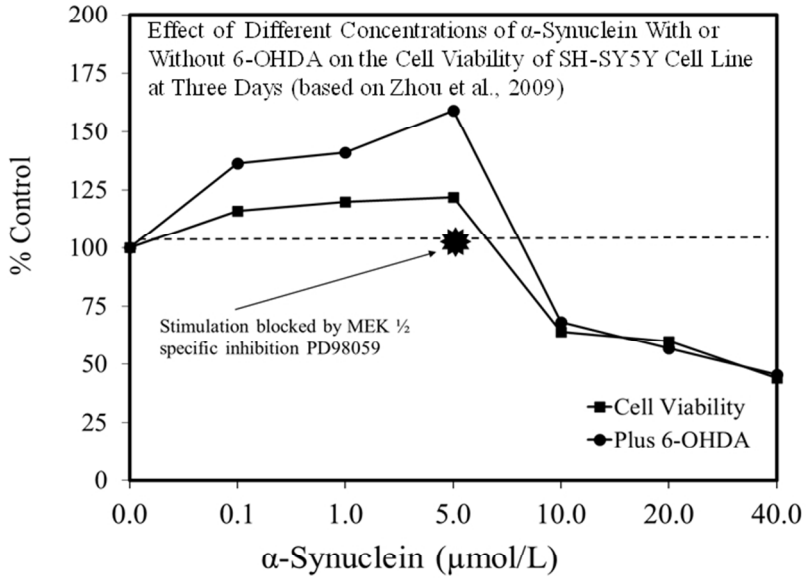

Figure 1 WW continued. Zhou et al 2009.

254x190mm (96 x 96 DPI)

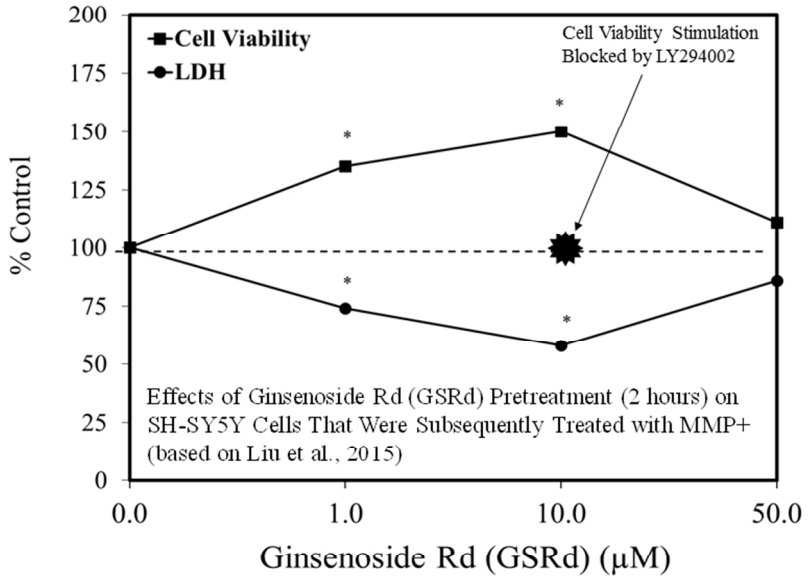

Figure 1X. Liu et al 2015.

254x190mm (96 x 96 DPI)

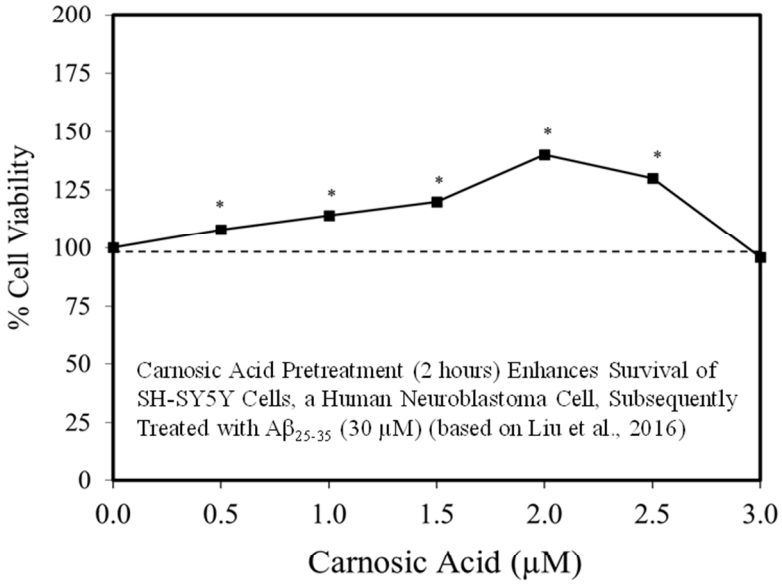

Figure 1Y. Liu et al 2016.

254x190mm (96 x 96 DPI)

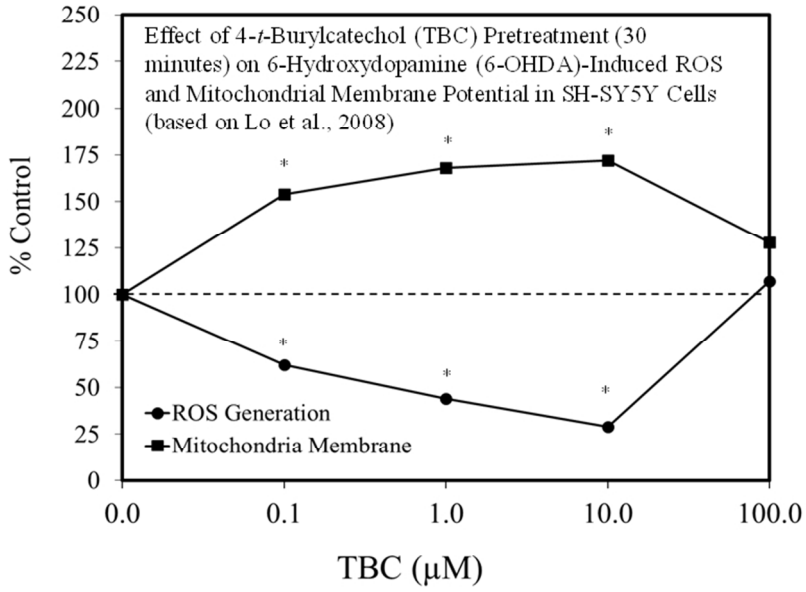

Figure 1Z. Lo et al 2008.

254x190mm (96 x 96 DPI)