International Journal of PharmTech Research
CODEN (USA): IJPRIF, ISSN: 0974-4304, ISSN(Online): 2455-9563
Vol.9, No.11, pp 29-37, 2016

Is Air Pollution A Leading Risk Factor For Stroke: A Review

Anjana Surendran[1], Shanmuga Sundaram Rajagopal[2]*, Krishnaveni Kandasamy[1], Sudha Muthusamy[1], Sambathkumar Ramanathan[3]

[1]Department of Pharmacy Practice, [2*]Department of Pharmacology, [3]Department of Pharmaceutics, J.K.K.Nattraja College of Pharmacy, Komarapalayam, India (Affiliated to Tamilnadu Dr. MGR Medical University, Chennai, India).

Abstract : A stroke is the sudden death of brain cells in a localized area due to inadequate blood flow/oxygen supply, either due to blockage or bursting of brain artery. Sudden loss of speech, weakness, or paralysis of one side of the body can be symptoms. Stroke is believed to be the second most common cause of death worldwide. Hypertension, smoking, high cholesterol, diabetes, cardiovascular disease, obesity and age are the prominent complications of stroke. An earlier study has documented a link between cardiovascular diseases(CVD) and air pollution. But recently conducted studies have established a correlation between air pollution and stroke. Pollutants emitted from industries, household, vehicles may form complex mixture and can be hazardous to human health. Several air pollutants like carbon monoxide(CO), sulphur dioxide(SO_2), nitrogen dioxide(NO_2), ozone(O_3) and fine particulate matter(PM)are found to be the major contributors to stroke. Fine particulate matter(PM) has a major role on human wellbeing and health than any other pollutant.

Keywords: Stroke, Air pollutants, CVD, Ischemia, Particulate matter, ROS.

Introduction

Neurodegenerative disorders are a very common problem in humans.[1] Stroke is predicted to be the second leading cause of death worldwide. Risk factors for stroke are diabetes mellitus, hypertension, smoking, alcohol consumption, decreased physical activity obesity etc. It has been reported in many studies that pollutants from the environment such as carbon monoxide (CO), ozone (O_3), nitrogen dioxide (NO_2), sulphur dioxide (SO_2),lead (Pb) and particulate matter (PM)are the leading causes of stroke.[2-4]Recent studies have substantiated and established a link between stroke and air pollution.[5]Though the mechanisms of interplay between stroke and environmental pollutants has not yet been fully elucidated, alterations in hemodynamic ,hemostatic factors and autonomic function may be the underlying pathology in debilitating cardiovascular disorders.[6-12]Chronic Obstructive Pulmonary Disease is now the fourth leading cause of death after cancer, heart attack and stroke. Thus stroke was the third leading cause of death.[13]

Stroke

A stroke is the sudden death of brain cells in a localized area due to inadequate blood flow/oxygen supply, either due to blockage or bursting of brain artery. Due to this blockage many complications like weakness, sudden loss of speech, paralysis of the body. Without blood to supply oxygen and nutrients and to remove waste products, brain cells quickly begin to die. Depending on the region of the brain affected, a stroke may cause paralysis, speech impairment, loss of memory and reasoning ability, coma, or death. A stroke also is

sometimes called a brain attack or a cerebrovascular accident (CVA). Stroke is a medical emergency requiring immediate treatment. Prompt treatment improves the chances of survival and increases the degree of recovery that may be expected. Types: Transient ischemic attack, Ischemic Stroke and Hemorrhagic stroke

a) Transient ischemic attack (TIA): Stroke occurring within a minute or short time and lasting for 24 hr is called as transient ischemic attack, and is a warning for future stroke attacks, cause due to narrowed carotid arteries, blood clots and atherosclerosis.

b) Ischemic Stroke (IS): Ischemic stroke is the most commonly occurring, as a result of blockage within the blood vessels of the brain hampering blood transport. These may happen due to: (1) cerebral embolism: plaque or blood clot fragment forms at another location this formed blood clot, which transports to brain through blood streams and which leads to ischemic stroke, (2) thrombotic stroke (TS):blood clot that formed within the artery of brain and (3) hemorrhagic stroke: less occurring as compared to ischemic stroke. As a result of any of such strokes, blood vessel of brain bursts or ruptures, leading to bleeding in brain surroundings. Chronic hypertension has been a major threat of hemorrhagic stroke. Hemorrhagic stroke is of 2 types: aneurysm hemorrhage and subarachnoid hemorrhage.[14]

Air Pollution

Pollution started from prehistoric times when man created the first fires. Air pollution comes from both natural and human-made (anthropogenic) sources. However, globally human-made pollutants from combustion, construction, mining, agriculture and warfare are increasingly significant in the air pollution equation. Motor vehicle emissions are one of the leading causes of air pollution.[15]Moreover, high blood pressure or hypertension is the most important and ubiquitous risk factor for heart attack and stroke, the leading causes of death worldwide. It's also found that the people living very close to large sound producing area such as Heavy Traffic Zone, Airport, heavy duty industries and so on having been diagnosed with high Blood pressure.[16]

Sources of free radicals causing air pollution:[17]

Sources of free radicals	**Mechanism**
Mitochondrial electron transport	leakage of superoxide due to inefficient reduction of O_2
Transition metal ions	Copper and iron facilitate hydroxyl radical formation
Inflammation	Free radicals released by activated phagocytes
Enzymes like xanthine oxidase	Release superoxide during reperfusion of ischemic tissues
Drug metabolism	Free radical intermediates created during metabolism
Cigarette smoking	**Gas phase reach in free radicals**
Radiation	X- rays and ultraviolet (UV) rays

It's a phenomenon that involves a sequence of events. Pollutants that are released from various sources like industry, from coal and petroleum, burning of fossil fuels and these pollutants which are contaminated by foreign substance transport and transformation in air atmosphere and they get effected on human beings and ecosystems.[18]

a) Ambient Air Pollutants and Stroke

Early studies have shown that a diet with less fruit, vegetables and whole grains, diets high in sodium, smoking, high BP, high BMI and diabetes are the risk factors for stroke and recent studies has added air pollution also as leading factors for stroke.[19]Air pollutants, emitted from various industries and households can cause various health-related problems like respiratory diseases[chronic pulmonary disease (COPD)], asthma and cardiovascular disease and the percentage of population affected with disease due to air pollution leading to death are about 16% of lung cancer death, 11% of COPD death and more than 20%ischemic heart disease (IHD)and stroke.[20]Studies shows carbon monoxide, fine particulate matters sulfur dioxide, nitrogen dioxide, and ozone are the air pollutants that cause stroke, of which fine particles have major role.[21,22]

b) Particulate Matter (PM)

Particulate matter (PM),a heterogeneous mixture of both liquid and solid particles of varying size, shape and chemical composition are suspended in air (Fig 1).The particles size of PM is very small, about<than

10 microns (micrometers) in diameter which can be inhaled. PM is of 2 types depending up on their size: (1) PM-10 particles and (2) PM-2.5 particles.

PM-10 particles with a diameter of 10 microns or less are usually generated by wind or mechanical agitation from cultivating PM 2.5 particles with of 2.5 microns diameter or less are generated from combustion and particles are often referenced as fine particles.

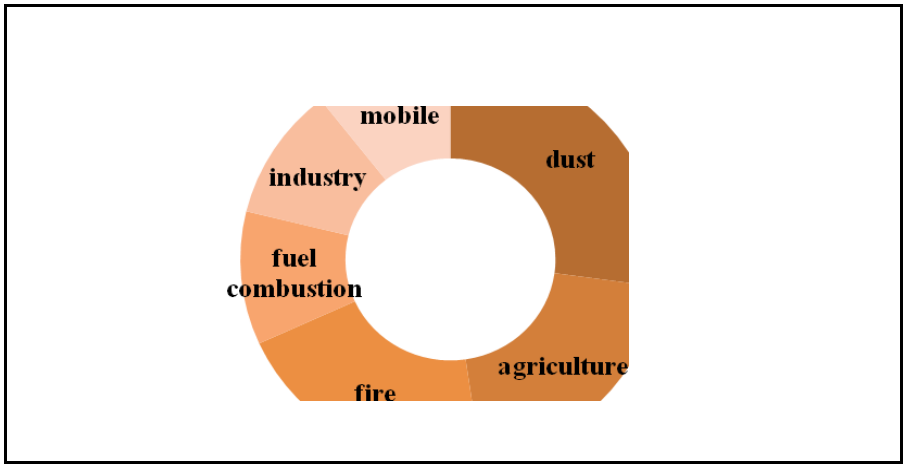

Figure No.1: Sources of air pollution particulate matter (PM) 10

There are 2 types of particles emitted by air pollution into atmosphere: (1) primary particles-that emits from wind, combustion, processes or by human activities directly to the atmosphere and (2) secondary particles-gaseous nitric acid and sulfur dioxide formed during the physicochemical transformation of nitrate and sulphate. In addition to these natural and anthropogenic sources of PM, others include particles from motor vehicle, road dust, industrial combustion, power generation, metal processing, agriculture, construction, wood burning, windblown soil and sea spray. The main constituents in all such sources include nitrates, organic compounds, sulfates, elemental and organic carbon.[23]

Air pollution (figure No.2), as sources of inflammation and oxidative stress, is prevalent in environmental source, contributing to the progression of stroke.[24,25]Nano particulate matter (nPM) emitted from vehicular exhaust may cause cerebral ischemia/reperfusion injury and cause up-regulation of inflammatory mediators and also generation of O_2 free radicals, resulting in regional micro-vascular failure and chronic environmental exposure to such pollutants may lead to progression of brain injury resulting in acute ischemic stroke.[26]

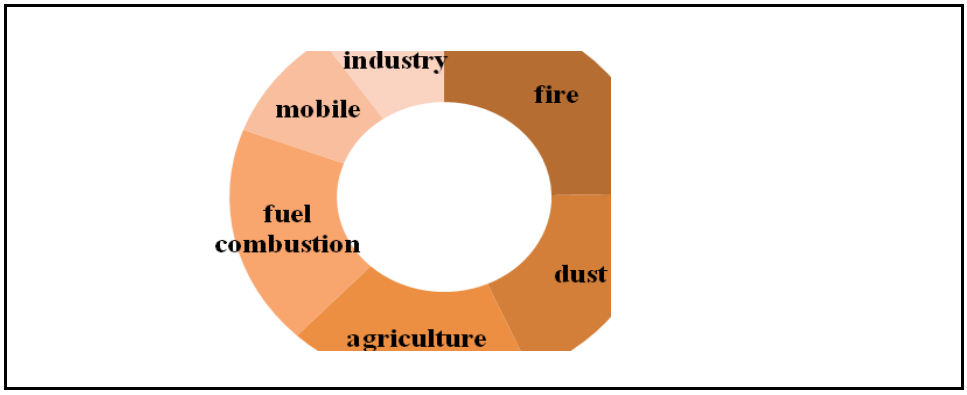

Figure No.2: Sources of air pollution for particulate matter (PM) 2.5

c) Carbon monoxide (CO)

CO, an odorless and colorless gas, is a product from carbon-containing fuels due to incomplete combustion (figure No.3). Other sources are motor vehicles/engines, chain saws, lawnmowers, improper gas-

burning/combustion and tobacco smoking. As CO has higher affinity for hemoglobin, CO reduces the oxygen-hemoglobin complex formation and therefore results in reduced oxygen delivery to the various body organs, leading to ischemia.[27,28] Binding of CO to hemoglobin(COHgb complex) can causes an allosteric change in the conformation of the oxyhemoglobin complex that increases the level of oxygen affinity of the remaining binding sites and this interferes with tissue level release of O_2.[29]

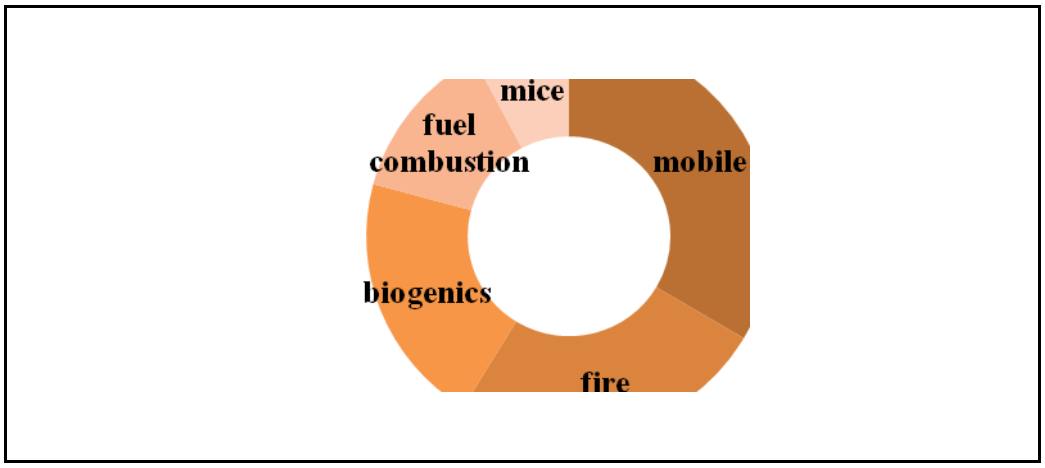

Figure No.3: Sources of carbon monoxide in air pollution

Although CO is produced naturally in human body as a signaling molecule, abnormality in the metabolism of CO is a risk factor for various diseases like blood pressure, inflammation, heart failure, and neurodegeneration. It has been reported than an increase in CO exhalation enhances the chances of (1) lowing brain volume, (2) increasing white matter volume and cerebrovascular vasodilation and,(3) increased cardiac output to maintain O_2delivery to the central nervous system(CNS)leading to cardiovascular hypoperfusion, (4) COHgb-mediated hypoxic stress and (5) intracellular oxidative disruption.[30-32]CO triggers brain lipid peroxidation which deposits peroxynitrite within blood vessel endothelium and brain parenchyma, leading to vascular compromise and cell death of neurons.[33,34]High levels CO have a greater risk of future transient ischemic stroke, especially in healthy adult.

d) Sulfur dioxide(SO_2)

Sulfur dioxide(SO_2), a highly irritating, colorless, soluble gas with pungent odor, forms sulfurous acid (H_2SO_3) upon reacting with water, is a strong acid that can cause irritant effects on eyes, mucous membranes and skin (figure No.4).[35]Sources of SO_2 are combustion of sulfur, mainly during power plants, diesel engines and metal sulfide ores. Sulfur dioxide which is oxidized into sulfur trioxide (SO_3), due to its affinity to water, it rapidly hydrated to form sulfuric acid((H_2SO_4).[36]

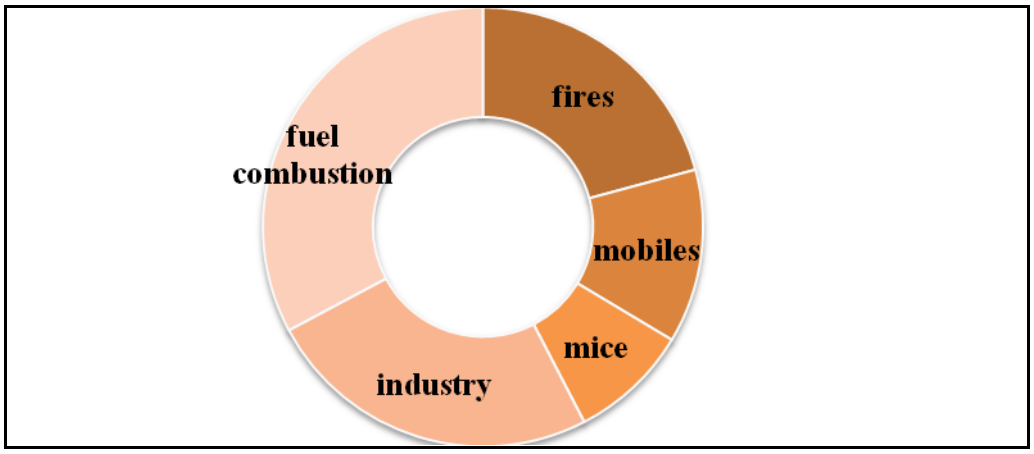

Figure No.4: Sources of Sulfur dioxide in air pollution

Inhalation of SO_2 may cause cerebrovascular health hazard, *viz.*, and cerebral ischemic accident.[37]Bronchoconstriction can occur upon exposure to SO_2, acidic compounds that are derived from CO and in all this, SO_2 appears as a toxic agent.[38-40]The biochemical pathway of SO_2 is to penetrate the brain's protective barrier leading tothe development of SO_2-mediated abnormal brain neural activity or brain ischemia.[41-43]

e) Nitrogen oxides (NOX)

Nitrogen oxides (NOXs) are reactive substances of nitric oxide (NO), nitrogen dioxide(NO_2), nitrogen trioxide (N_2O_3), nitrogen tetroxide (N_2O_4) and dinitrogenpentoxide (N_2O_5). These compounds are referred to collectively as NOX. Gaseous nitric acid (HNO_3)is the most vital source of particulate nitrate (figure No.5).Other members of NOXs are nitrous acid (HNO_2), nitrous oxide (N_2O), peroxyacetyl nitrates ($C_2H_3NO_5$), nitrites (NO_2), nitrosocompounds (R-N=O) and nitrogen-containing acids (N_2).[44]

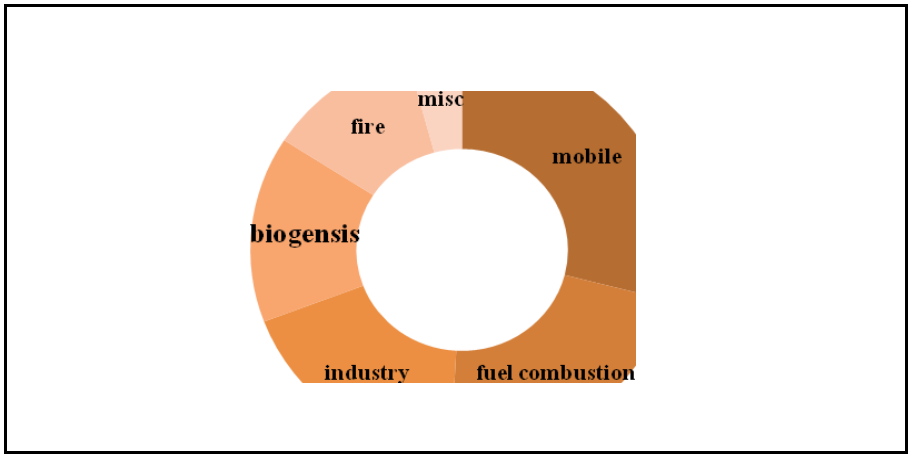

Figure No.5: Source of nitrogen dioxide in air pollution

Cerebral ischemia induces multiple and distinct changes in cerebral NO content, signaling occlusion in middle cerebral artery occurring due to increased production of NO,[45,46] reducing the brain tissue NO to below detectable level,[47]indicating that a long lasting NO deficiency in ischemic brain can cause a chronic phase after cerebral ischemia angiogenesis and this may extend to a collateralization with neurological outcome after stroke.[45-49]

f) Ozone (O_3)

Ozone (O_3), a highly reactive, colorless-to-bluish gas, odor associated with electrical discharges is formed due to natural processes as well as human activities(figure No.6).[50]It is also formed as a result of solar radiation on molecular oxygen (O_2) in the stratosphere. It will prevent high-energy UV radiation from penetrating the atmosphere, as O_3 is the chief constituent of photochemical smog. The sources of O_3 are as a result of action of solar UV radiation on nitrogen oxides and reactive hydrocarbons produced in troposphere, emitted from vehicles and many industrial sources.[51]

The effects of O_3 pollution on healthy population are oxidative stress, systemic inflammatory responses and blood coagulation.[52-53]Thephenomena that are induced by low down rank of O3 could be a trigger for ischemic event to atherosclerotic plaque instability, endothelial dysfunction leading to increased coagulation and thrombosis.[54]

g) Second-hand, Mainstream and Side stream smokes

Second-hand smoke (SHS) is otherwise known as environmental tobacco smoke. SHS formed during burring of tobacco. Mainstream smoke is the smoke exhaled by a smoker. Sidestream smoke: lighted end of a cigarette producing smoke, both the smokes causing cancer as particles size is very small as compared to mainstream smoke. When non-smokers get exposed to these smoke, they breathe in nicotine and toxic

chemicals, at the same level as a smoker do. The health of non-smokers getting exposed to a second hand smoker at work, at home or even in publicare the same as the smoker gets affected.[55,56]

SHS has a keyfeatur ein causing chronic diseases like lung cancer, asthma, heart disease but recently studies have shown that there a link between SHS and stroke.[57]

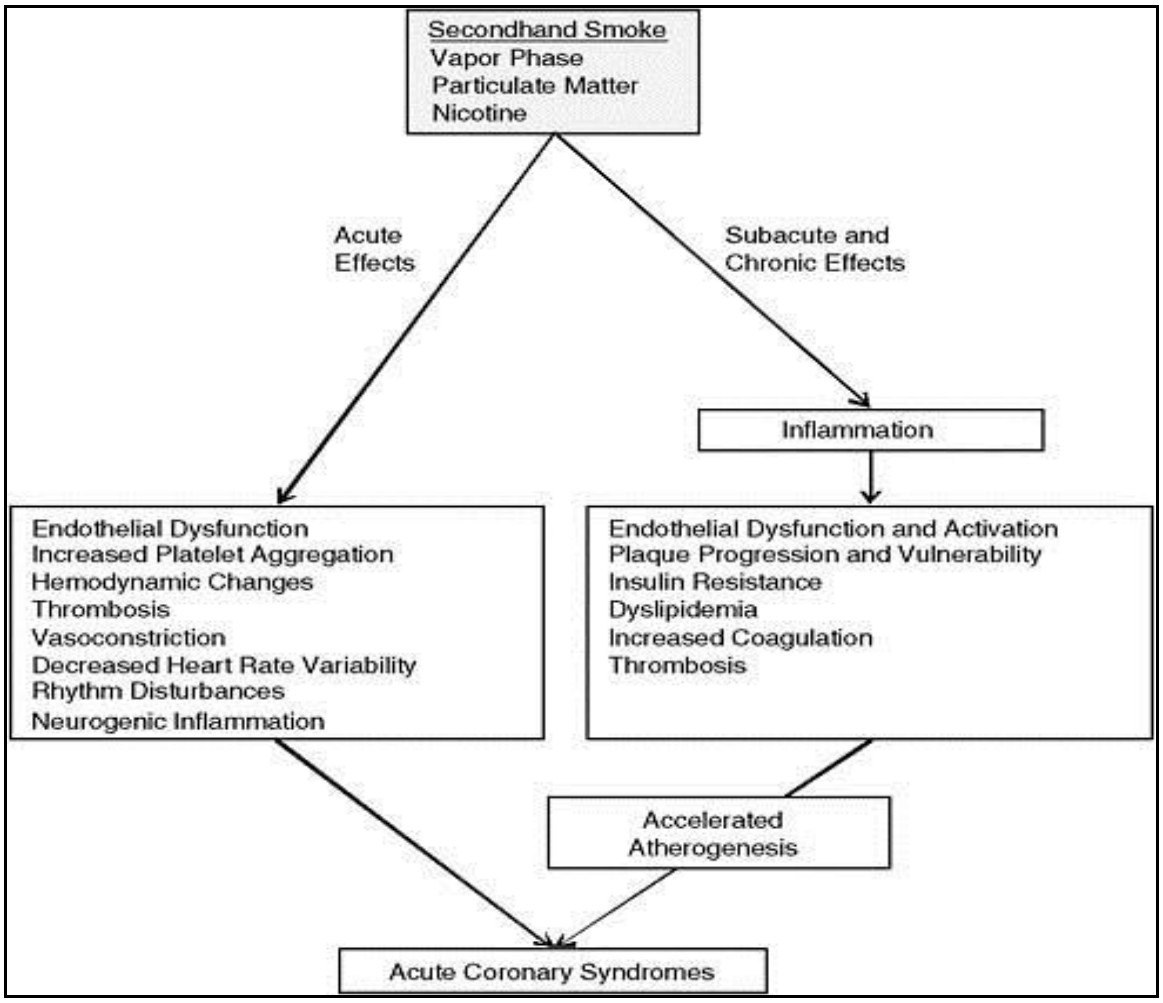

Figure No.6: Complication of second hand smoke (SHS)

Conclusion

Stroke, which is common in middle-aged and elderly, is one of the leading causes, especially in patients with risk of hypertension, diabetes mellitus, dyslipidemia, smoking, excessive alcohol consumption and atherosclerosis. Cardiovascular diseases are the leading cause of deaths on the globally, which also leads to stroke.[58]Sulphur dioxide, nitrogen dioxide and CO as air pollutants were found to increase the risk for stroke.

Among these air pollutants, it has been found that exposure to PM2.5has been the most dangerous, as exposure to just two days to such pollutants, can create risk for stroke. Fine particles formed due to the reactions between atmosphere gases, dominate the inhalable particulate fraction, gaseous pollutants include$SO_2$and $NO_2$and may be good markers for such particles. Free radicals produced from air pollution can cause inflammatory responses which enhances blood coagulation and increase plasma viscosity, leading to ischemic stroke but not to hemorrhagic stroke. Moreover, medicinal plants through their active ingredients have a good therapeutic effect of diseases and disorders in attenuating air pollution-related health hazards.[59,60]

Conflict of Interest

The authors have no conflict of interest.

References

1. Prabhakar S, Taranjeet K, Ashish T. Role of active components of Medicinal plants in Neurodegenerative disorders and Synaptic Plasticity, International Journal of ChemTech Research, 2014, 6: 982-984.
2. Pope CA, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, Goldleski JJ. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. Circ., 2004, 109:71-77.
3. Pope CA, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, Thurston GD. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution.JAMA.,2002, 288: 1132-1141.
4. Samet JM, Dominici F, Curriero FC, Jonathan M, Ivan C, Scott LZ. Fine particulate air pollution and mortality in 20 U.S. cities, 1987–1994. N Engl J Med., 2000, 343: 1742-1749.
5. Pope CA. Mortality and air pollution: associations persist with continued advances in research methodology. Environ Health Perspect.,1999, 107: 613-14.
6. Pope CA, Dockery DW, Kanner RE, Villegas GM, Schwartz J. Oxygen saturation, pulse rate, and particulate air pollution: A daily time-series panel study. Am J RespirCrit Care Med., 1999, 159: 365-3672.
7. Zanobetti A, Canner MJ, Stone PH, Schwartz J, Sher D, Eagan EB et al. Ambient pollution and blood pressure in cardiac rehabilitation patients. Circ., 2004, 110: 2184-2189.
8. Ghio AJ, Kim C, Devlin RB. Concentrated ambient air particles induce mild pulmonary inflammation in healthy human volunteers. Am J RespirCrit Care Med., 2000, 162: 981-988.
9. Schwartz J.Air pollution and blood markers of cardiovascular risk. Environ Health Perspect, 109, 2001, 405-409.
10. Riediker M, Cascio WE, Griggs TR, Herbst MC, Brombery PA, Neas L et al. Particulate matter exposure in cars is associated with cardiovascular effects in healthy young men.Am J RespirCrit Care Med., 169, 2004, 934-940.
11. Gold DR, Litonjua A, Schwartz J, Lovett E, Larson A, Nearing B et al. Ambient pollution and heart rate variability. Circ., 2000, 101: 1267-1273.
12. Creason J, Neas L, Walsh D, Williams R, Shelon L, Liao D et al. Particulate matter and heart rate variability among elderly retirees: the Baltimore 1998 pm study. J Expo Anal Environ Epidemiol.,2001, 11: 116-122.
13. Sanjana T, Lakshmi T. Role of Echinacea purpurea for COPD management –A Mini Review. Int J PharmTech Res., 2013, 5: 1808-1810.
14. Schneider AT, Pancioli AM, Khoury JC, Rademacher E, Tuchfarber A, Miller R et al. Trends in community knowledge of the warning signs and risk factors for stroke.JAMA.,2003, 289: 343-346.
15. Prasad C, Santa Rao K, GovindaRao P. Thermoelectric Power Generation by recovering heat energy from the exhaust gases: A Green Technology approach, International Journal of ChemTech Research., 2016, 9: 577-584.
16. Gayathri K, AmuthaJaisheeba A, Sornaraj R.Physical and Cardiovascular Implications of Noise Pollution prevailed in Thoothukudi the Industrial City, Tamilnadu, India., International Journal of ChemTech Research, 2012, 4: 1223-1228.
17. SachinUttamRakesh, Priyanka R Patil, Sagar R Mane. Use of Natural Antioxidants to Scavenge Free Radicals: A Major Cause of Diseases. International Journal of PharmTech Research, 2010, 2: 1074-1081.
18. Beachler DS, Joseph GT. Emission regulations and air pollution control equipment for industrial and utility boilers.EnviroProg., 1984, 3: 44-50.
19. Dominici F, McDermott A, Daniels D, Samet JM, Ramsay TO, Zeger SL. Mortality among residents of 90 cities. In: Special report: Revised analyses of time-series studies of air pollution and health. Boston, Mass. Health Effects Institute, 2003, 9: 24-28.

20. John HS. Atmospheric chemistry and physics: From air pollution to climate change. New York, NY: John Wiley & Sons, 1998.
21. Hong YC, Lee JT, Kim H, EH Ha, J Schwartz, DC Christiani. Effects of air pollutants on acute stroke mortality. Environ Health Perspect., 2002, 110: 187-191.
22. Hong YC, Lee JT, Kim H, Kwon HJ. Air pollution: a new risk factor in ischemic stroke mortality. Stroke, 2002, 33: 165-2169.
23. Daigle CC, Chalupa DC, Gibb FR, Morrow PE, Oberdorster G, Utell MJ et al. Ultrafine particle deposition in humans during rest and exercise.InhalToxicol., 2003, 15: 539-552.
24. Block ML, Calderon-Garciduenas L. Air pollution: mechanisms of neuroinflammation and CNS disease. Trends Neurosci., 2009, 32: 506-16.
25. Craig L, Brook JR, Chiotti Q, Croes B, Gower S, Hedley A et al. Air pollution and public health: a guidance document for risk managers. J Toxicol Environmental Health-Part A., 2008, 71: 588-598.
26. Guo L, Li B, Miao J, Yun Y, Li G, Sang N. Seasonal variation in air particulate matter (PM) exposure induced ischemia-like injuries in the rat brain.Chem Res Toxicol., 2014, 51: 788-790.
27. Hampson NB, Norkool DM. Carbon monoxide poisoning in children riding in the back of pickup trucks.JAMA., 1992, 267: 538-540.
28. Hagberg M, Kolmodin-Hedman B, Lindahl R, Nilsson CA, Norstrom A. Irritative complaints, carboxyhemoglobin increase and minor ventilatory function changes due to exposure to chain-saw exhaust.Eur J Respir Dis., 1985, 66: 240-247.
29. Seger DL, Welch LW. Carbon monoxide. In: Sullivan JB. Clinical environmental health and toxic exposures. 2001, 78: 722-727.
30. Benignus VA, Petrovick MK, Newlin-Clapp L, Prah JD. Carboxyhemaglobin and brain blood flow in humans.NeurotoxicolTeratol, 1992, 14: 285-290.
31. Lee MS, Marsden CD. Neurological sequelae following carbon monoxide poisoning clinical course and outcome according to the clinical types and brain computed tomography scan findings.MovDisord., 1994, 9: 550-558.
32. Raub JA, Benignus VA. Carbon monoxide and the nervous system.NeurosciBiobehav Rev., 2002, 26: 925-940.
33. Harrison RM. Measurements of concentrations of air pollutants. In: Holgate ST, Samet JM, Koren HS, eds. Air pollution and health. San Diego, Calif: Academic Press; 1999, 63-81.
34. Bell JD. Molecular cross talk in traumatic brain injury. J Neurosci., 1992, 73: 1584-1589.
35. Lipsett MJ. Ozone. In: Sullivan, Clinical environmental health and toxic exposures. 2001, 54: 806-818.
36. World Health Organization. Air Quality Guidelines ForEurope. WHO regional publications, European series No.23. Copenhagen, Denmark: World Health Organization, 1987.
37. Joubert J, Cumming TB, McLean AJ. Diversity of risk factors for stroke: the putative roles and mechanisms of depression and air pollution, J Neurological Sci, 71, 2007, 1-2.
38. Atkinson RW, Anderson HR, Strachan DP, Bland JM, Bremner SA, Ponce de Leon A. Short-term associations between outdoor air pollution and visits to accident and emergency departments in London for respiratory complaints.EurRespir J., 1999, 13: 257-265.
39. Rossi OVJ, Kinnula VL, Tienari J, Huhti E. Association of severe asthma attacks with weather, pollen, and air pollutants.Thorax., 1993, 48: 244-248.
40. Thurston GD, Ito K, Lippmann M, Hayes C. Re-examination of London, England, mortality in relation to exposure to acidic aerosols during 1963–1972 winters. Environ Health Perspect., 1989, 79: 73-82.
41. Bates DV, Sizto R. Air pollution and hospital admissions in Southern Ontario: the acid summer haze effect. Environ Res., 1987, 43: 317–331.
42. Ware JH, Ferris BG, Dockery DW. Effects of ambient sulfur oxides and suspended particles on respiratory health of preadolescent children.Am Rev Respir Dis., 1986, 133: 834-842.
43. Sunyer J, Ballester F, Le Tertre A, Atkinson R, Ayres JG, Forastiere F et al. The association of daily sulfur dioxide air pollution levels with hospital admissions for cardiovascular diseases in Europe.Eur Heart J., 2003, 24: 8752–8760.
44. US Environmental Protection Agency. Air quality criteria for oxides of nitrogen. Vol. I. Research triangle park, NC: US Environmental protection agency, 1993, 3-14.
45. Malinski T, Bailey F, Zhang ZG, Chopp M. Nitric oxide measured by a porphyrinic micro sensor in the rat brain after transient middle cerebral artery occlusion. J Cereb Blood Flow Metab., 1993, 13: 355-358.

46. Kader A, Frazzini VI, Solomon RA, Trifiletti RR. Nitric oxide production during focal cerebral ischemia in rats.Stroke., 1993, 24: 1709-1716.
47. Sugimura X, Sako K, Tohyama Y, Yonemasu Y. Consecutive *in vivo* measurement of nitric oxide in transient forebrain ischemic rat under normothermia and hypothermia. Brain Res., 1998, 808: 313-316.
48. Beck H, Plate KH. Angiogenesis after cerebral ischemia.ActaNeuropathol., 2007, 117: 481-496.
49. Cristoforidis GA, Mohammad Y, Kehagias D, Avutu B, Slivka AP. Angiographic assessment of pial collaterals as a prognostic indicator following intra-arterial thrombolysis for acute ischemic stroke. Am J Neuroradiol., 2005, 26: 1789-1797.
50. Lipsett MJ. Ozone. In: Sullivan. Clinical environmental health and toxic exposures. 2001, 2: 806-818.
51. US Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment. Air quality criteria for ozone and related photochemical oxidants. Washington, DC: US Environmental Protection Agency; 1996. Publication No. EPA/600/P-93/004a-cF. Available from: <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid2831>[Accessed June 25, 2016].
52. Chuang KH, Chan CC, Su TC, Lee CT, Tang CS. The effect of urban air pollution on inflammation, oxidative stress, coagulation and autonomic dysfunction in young adults.Am J RespirCrit Care Med., 2007, 176: 370-386.
53. Jang AS, Choi IS, Yang SY, Kim YG, Lee JH, Park SW et al. Antioxidant responsiveness in BALB\c mice exposed to ozone.Respir., 2005, 72: 79-84.
54. Neill MS, Veves A, Zanobetti A, Sarnat JA, Gold DR, Economides PA et al. Diabetes enhances vulnerability to particulate air pollution-associated impairment in vascular reactivity and endothelial function. Circ., 2005, 111: 2913-2920.
55. Karim ZA, Alshbool FZ, Vemana HP, Adhami N, Dhall S, Espinosa EV et al. Third-hand smoke: impact on haemostasis and thrombogenesis. J Cardiovasc Pharmacol., 2015, 66: 177-1782.
56. Moon KA, Magid H, Torrey C, Breysse PN. Second-hand smoke in water pipe tobacco venues in Istanbul, Moscow and Cairo. Environ Res., 2015, 142: 568-574.
57. US Environmental Protection Agency, Office of Research and Development, Office of Health and Environmental Assessment. Respiratory health effects of passive smoking (also known as exposure to second hand smoke or environmental tobacco smoke-ETS). Washington, DC: US Environmental Protection Agency; 1992. Available from: <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid2835>. [Accessed June 25, 2016].
58. Jasmine R, Sakthivel H. Role of compounds from *Terminalia chebula* exhibiting anti-cholesterol property. International Journal of PharmTech Research., 2015, 8: 210-215.
59. Mallick M, Bose A, Mukhi S. Comparative evaluation of the antioxidant activity of some commonly used spices. International Journal of PharmTech Research, 2016, 9: 1-8.
60. Mohammad Reza MahmoudianSani, Majid Asadi-Samani, Ali Saeedi-Boroujeni, Mehdi Banitalebi-Dehkordi, Mahmoud Bahmani. Suppressive effects of medicinal plants and their derivatives on inflammatory complex: a systematic review. International Journal of PharmTech Research, 2016, 9: 325-333.

*****