

# High Prevalence of Stunting and CKD-1/Obesity in Low- and Middle-nSES Population: A Review Article Support by p53-p21-p16 Axis

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## Abstract—

**Introduction:** Stunting /pygmy or growth impairment parallel with obesity, is in high prevalence in the Aflatoxins exposure population, based on p16 upregulation. Mutation of p16 or epigenetic silencing, gives proliferation of BAT (UCP 132), SMCs (CKD-1), and later cancer cell proliferation and metastasis.

**Method:** Review articles using my Library, and academic search engines like PubMed, Science Direct, and EBSCOhost. Keywords searching use Stunting-AFB1 exposure (23 Systematic Reviews), and Meta-Analysis (MA) ^ stunting (7), urine AFM1 (82) sub ppb, MA p16 upregulated (35). Acute exposure is excluded. Bayesian Analytical is used to find the reference that supports the p53-p21-p16 axis in AFB1exposure, which causes stunting in low- and middle- neighborhood Socioeconomic Status/nSES populations.

**Result:** One figure and 3 tables of Senescence barrier, AFB1-stunting, MA p53 axis-stunting, MA p16 upregulation-stunting, and p16 downregulation-cancer.

**Discussion:** p16 upregulated in stunting then in the older years p16 mutation or epigenetic silencing in proliferation cells due to the senescence barrier.

**Conclusion:** Detect in the population by epidemiology, laboratory in sub ppb, anthropometric measurement, and anamnesis survey where the refrigerator is full of leftover food, on winning to fight stunting.

**Keywords—** Stunting, AFB1 exposure, Urine AFM1, Pygmy, p53-p21-p16 axis.

## I. INTRODUCTION

There is an urgent need to inform the public and political decision-maker (mainly the legislative) to lead people to mitigate AFB1exposure, and promote the technique in preparing clean food, and the useful of good food stuff management<sup>1,2,3,4</sup> in fighting most diseases<sup>5,6,7,8</sup> especially stunting in low- and middle-neighborhood Socioeconomic Status (nSES) population.<sup>9</sup> The people should throw away the AFB1 exposure food which is not success to do until now.<sup>10,11</sup> Moreover, don't give it to animals because Aflatoxin doesn't destruct with high temperatures till 250°C and metabolite to AFM1.<sup>11</sup>

Stunting/pygmy or growth impairment, associated with the p53-p21-p16 axis has been broadly known. This study focuses on upregulated p16<sup>9,12,13</sup> as tumor suppressor induce growth impairment mechanism, not the later stage which knock out of p16, induced proliferation.<sup>14,15,16,17,18,19,20,21</sup> and cancer.<sup>22</sup> Post-weaning associated with stunting<sup>23</sup> and paradox downregulation,<sup>24</sup> has been reported.

Stern, 2001, has reported p53 mutation codon 249 in HCC patients in China (AFB1 Meta-Analysis).<sup>19</sup>

Leong, 2009: downregulated p53 induced upregulated p16 (p53-p21-p16) axis pathway.<sup>14</sup>

## II. METHOD

A review of articles on the prevalence of stunting and obesity in low- and middle-nSES areas by the p53-p21-p16 axis is built. Systematic Reviews and Meta-Analysis references are preferable when using my library and search engine EBSCOhost, ScienceDirect, and others while chasing academic references. Focus on p16 upregulated-stop the cell cycle growth using Bayesian network and analysis. Keywords searching use Stunting-AFB1 exposure (23 Systematic Reviews), and Meta-Analysis (MA) ^ stunting (7), urine AFM1 (82) sub ppb, MA p16 upregulated (35). Acute exposure is excluded.

## III. RESULT

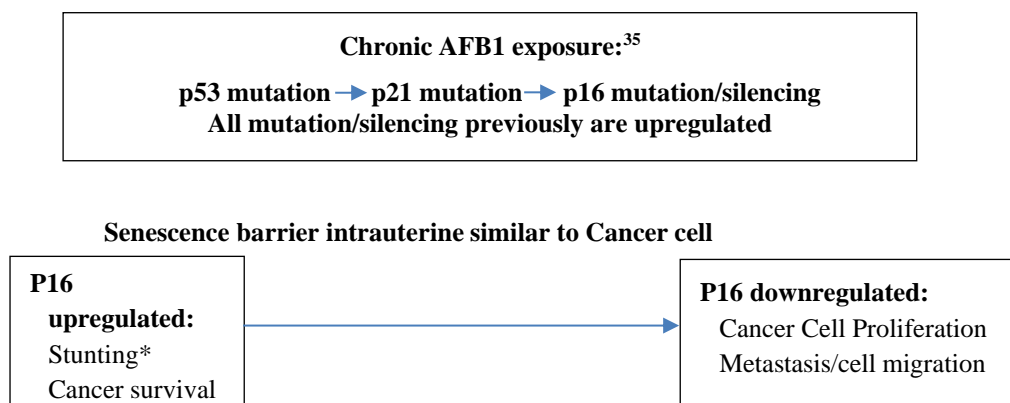
P16 or P16-INK4A also known as CKDI 2A gene upregulated by p53 and p21 mutation due to AFB1 exposure. In this low- and middle- nSES population, epidemiology of stunting and obesity, and later Diabetes Mellitus are in high prevalence.<sup>11</sup> Downregulated p16 which gives proliferation at a later age, becomes controversial while upregulated p16, which gives stops the cell cycle (stunting).<sup>15</sup> Epidemiology of both (stunting-obese), parallel happen in the same area.<sup>12,25</sup> This study reveals the upregulated p16 in the younger age, while in the older, obesity is in high prevalence too. It includes Diabetes Mellitus underlying CVD/CHD as the cause of death, and other complication of diabetes. In another sentence, in the high prevalence of stunting, adult people: the parents, executive, and legislative, are at high prevalence of Obesity, Diabetes, and CVD, similar with reported by Smith.<sup>25</sup> By AFB1 induced p53-p21-p16 axis, firstly, all cases of up-regulated p16 inhibit proliferation such as cancer, also specific induce growth impairment are chased.<sup>26,27,28</sup>

Up-regulated of p16 by miR-877-3p inhibits the proliferation of bladder cancer.<sup>29</sup>

The p16-dependent upregulation of PD-L1 impairs immunosurveillance of senescence cells.<sup>30</sup> Upregulated p16 inhibit cycle's G1/S in cancer, stimulus direct or indirect has been reported.<sup>20,21,22,31,32</sup>

The p53-p16 axis is a senescence pathway in mouse and human cells.<sup>20</sup>

Whereas p16INK4a overexpression is a marker for survival/good prognosis/low grade in cancerous patients (Meta-Analysis).<sup>33</sup> Also overexpression was reported in good outcomes of cancer,<sup>22,32</sup> and mastocytosis (urticarial pigmentosa).<sup>34</sup> And Alternative reading frame protein (ARF) is a novel protein in activating p53.<sup>21,31</sup>



**FIGURE 1. Pathogenesis of stunting from molecular pathways mechanism p53-p21-p16 axis**

*\*Upregulated p16 inhibit cycle's G1/S in cancer, stimulus direct or indirect has been reported*

## IV. DISCUSSION

Many scientists have revealed that pygmy and small stature is simply a genotype factor geographical area, and with the imported food and feed, developed countries also have prone to a little stature Caucasian.<sup>11</sup> In Table 1. Aflatoxin effect on stunting and

since good nutrition and micronutrient fail to fight stunting,<sup>37</sup> pay attention change to find AFB1 in food which is metabolite to AFM1 and on urine could be as AFB1 exposure marker.<sup>47,5,6,7,47,49,50,54,58,61,62,63</sup>

**TABLE 1**  
**DESCRIPTION OF IDENTIFIED 18 LITERATURES ON AFLATOXIN EXPOSURE-STUNTING, BUT NEGLECTED AND ABANDONED IN MOST COUNTRIES**

Study, year	Mutation p53, p21, p16 upregulation	Stunting population	Aflatoxin exposure	Countries
<sup>9</sup> Miller, 2016	Stern 2001 Leong 2009	Meta-analysis Stunting and child development	Peni Oct 2018	15 low- and middle-income countries
<sup>12</sup> Sousa, 2016	Stern 2001 Leong 2010	Stunting and overweight	Brazilian	Brazilian
<sup>36</sup> Olivero, 2016	Stern 2001 Leong 2011	Pygmies	Tropical rainforest	Central African forest
<sup>2</sup> Smith 2012	Stern 2001 Leong 2012	Impaired growth/stunting senescence	Food chain mycotoxin	Developing countries
<sup>3</sup> Smith LE, 2015	Stern 2001 Leong 2013	Stunting Child undernutrition Likelihood of being overweight, CVD, diabetes	Mycotoxins contributor	SHINE Trial
<sup>25</sup> Smith LC, 2015	Stern 2001 Leong 2014	Child undernutrition Likelihood of being overweight, CVD, diabetes	Not mention	116 countries
<sup>37</sup> Watson, 2015	Stern 2001 Leong 2015	Undernourished child	May be undermined by dietary Exposure to Aflatoxin	Targeting Child undernutrition in developing Countries
<sup>38</sup> Watson 2016	Stern 2001 Leong 2016	Young children Micronutrient Status	Dietary aflatoxin exposure	Guinea
<sup>39</sup> Knipstein, 2015	Stern 2001 Leong 2017	Induced stunting and liver injury	Dietary Aflatoxin	Rat model
<sup>40</sup> Wild CP, 2015	Stern 2001 Leong 2018	Cancer and Stunting	Mycotoxin control	Low- and Middle-income countries
<sup>41</sup> Wild CP, 2007	Stern 2001 Leong 2019	Growth impairment/stunting	Aflatoxin exposure	Developing countries
<sup>8</sup> Ezekiel, 2014	Stern 2001 Leong 2020	Children, adolescents adult	LC-MS/MS multi biomarker	Rural North Nigeria
<sup>42</sup> Lombard, 2014	Stern 2001 Leong 2021	Infant and young child growth	Mycotoxin exposure	Africa
<sup>43</sup> Khlangwiset, <sup>2011</sup>	Stern 2001 Leong 2022	Growth impairment Stunting and underweight	Aflatoxin in utero also	Less developed countries
<sup>44</sup> Gong, 2012	Stern 2001 Leong 2023	School children	Chronic hepatomegaly	Kenyan School Children
<sup>23</sup> Gong, 2004	Stern 2001 Leong 2024	Impaired child growth	Post weaning exposure to aflatoxin	Benin, West Africa
<sup>45</sup> Gong, 2003	Stern 2001 Leong 2025	Critical role of weaning in youngchildren	Determinants of aflatoxin exposure	Benin and Togo
<sup>46</sup> Stevens, 2012	Stern 2001 Leong 2026	Mild, moderate and severe stunting	Peni Oct 2018: AFB1 exposure	141 developing countries

<sup>19</sup>Stern 2001: p53 mutation codon 249 in HCC patients in China (AFB1 Meta-Analysis)

<sup>14</sup>Leong 2009: downregulated p53 → upregulated p16 (p53-p21-p16 axis pathway)

**TABLE 2**  
**DESCRIPTION OF 17 REFERENCES OF URINE AFLATOXIN M1 AS METABOLITE OF AFB1 EXPOSURE, IN P53-P21-P16 AXIS PATHWAYS**

Study, year	Patients	Urine AFM1	Countries	P53, p21, p16
<sup>19</sup> Stern, 2001	HCC, Meta- analysis	AFB1 exposure	China	P53 -codon 249 mutation
<sup>20</sup> Wadhwa, 2004	Senescence mouse and human cells	P53-p16 signaling	Japan	P53, p16
<sup>21</sup> Hasan, 2002	Senescence cell of Mouse and human	Activating p53	Japan	P16-p21-p53
<sup>47</sup> Ali, 2016	AFB1	Urine AFM1	Rural vs. urban Bangladesh	P53 mutation
<sup>5</sup> Gerding, 2014	AFB1	Urine AFM1	Bangladesh Haiti	P53 mutation
<sup>7</sup> Jager, 2016	AFB1	Urine AFM1	Brazil	P53 mutation
<sup>8</sup> Ezekiel, 2014	Cross-sectional communities	Multibiomarker morning urine	Rural Northern Nigeria	P53 mutation
<sup>48</sup> Warth, 2012	AFB1	Urine AFM1	Cameroon	P53 mutation
<sup>49</sup> Warth, 2014	AFB1	4 urine biomarkers	Bangkok	P53 mutation
<sup>6</sup> Mitchel, 2013	AFB1	Urine AFM1	Ghana	P53 mutation
<sup>50</sup> Solfrizo, 2011	AFB1	Urine AFM1 biomarkers	Human and pig	P53 mutation
<sup>51</sup> Solfrizo, 2014	AFB1	Urine AFM1	Southern Italy	P53 mutation
<sup>26</sup> Romero De Cassia, 2009	AFB1	Urine AFM1	Brazilian	P53 mutation
<sup>52</sup> Jonsyn F, 1995	AFs in cord blood pregnant 58%	Urine AFM1 No	Sierra Leone	P53 mutation
<sup>53</sup> Jonsyn FE, 1999	AFB1	Urine sample were 100% contaminated	Infants in Sierra Leone	P53 mutation
<sup>54</sup> Jonsyn E, 2007	AFB1	Urine AFM1	Boys and Girls Sierra Leone	P53 mutation
<sup>55</sup> Chen, 2017	AFB1 infant rice cereal	Aptamer AFB1	Detection AFB1	P53 mutation

**TABLE 3**  
**DESCRIPTION OF 12 IDENTIFIES LITERATURES ON META-ANALYSIS (MA) OF P16INK4A UPREGULATION, SENESCENCE BARRIER, AND DOWNREGULATION**

Study, year	MA	Upregulated P16	Stunting	Cancer/Proliferation
<sup>20</sup> Wadhwa, 2004	P53 Signaling	The ARF-p53 in mouse and human		Senescence pathway
<sup>56</sup> Xiao, 2016	MA	Promoter methylation		Ovarian cancer
<sup>57</sup> Wang, 2016	MA	Overexpressed p16: prognosis		Esophageal squamous cell carcinoma
<sup>58</sup> Cao, 2016	MA	Overexpressed p16		Vulvar cancer
<sup>59</sup> Yifan, 2015	MA	Promoter methylation		Lung cancer diagnostic
<sup>33</sup> Bu, 2014	MA	Overexpression p16: survival		Osteosarcoma
<sup>31</sup> Hasan, 2004	P53 Signaling	CARF-p53		Negative Feedback control
<sup>9</sup> Miller, 2016	MA	Low- and middle- income countries	Stunting	Multidimensional Child development
<sup>12</sup> Sousa, 2016	SR and MA	Brazilian children	Stunting	Overweight/obesity
<sup>60</sup> Altare, 2016	MA	Emergency pockets: Ethiopia	Child wasting	
<sup>13</sup> McDonald, 2013	MA	Developing countries	Multiple anthropometric deficits	Child mortality
<sup>19</sup> Stern, 2001	MA	China: AFB1-p53 codon 249 mutation		HCC patients

Stunting or pygmy is due to high and chronic exposure to AFB1 which metabolites to AFM1, which is parallel to high prevalence in central Africa.<sup>36</sup> Mitigation of AFB1 exposure by avoiding wet and warm storage rooms, but is also had thought as others approach to decrease aflatoxin exposure by gamma ray,<sup>65</sup> culture, and lifestyle.<sup>36,62,66</sup> WHO guidelines<sup>67</sup> give the tolerable daily intakes used by governments and international risk managers to establish maximum levels for mycotoxins in food. The maximum levels for mycotoxins in food are very low due to aflatoxin severe toxicity. This study supports WHO by recording the argumentation to fight AFB1 exposure that induces stunting in low- and middle-nSES. It is as follows:

#### **4.1 Reducing P16 increase proliferation, upregulated p16 induced stunting:**

Upregulated in younger age, then downregulated in older age after experiencing of Senescence barrier phase. The senescence barrier could be intrauterine due to maternal mycotoxin exposure and adverse pregnancy outcomes,<sup>52,68</sup> pregnant women,<sup>42,51,52,69</sup> which have associated with growth impairment.<sup>3,8,42,43,70</sup> emphasize that AFB1, especially in utero, is associated with DNA methylation in white blood cells of infants in the Gambia.<sup>70</sup> Table 3. Review the sequence of upregulated p16 which induced stunting, through the senescence barrier phase,<sup>20</sup> with the silencing/reducing p16 (downregulated p16) induced proliferation such as overweight and obesity,<sup>12</sup> and cancer.<sup>14,19</sup>

#### **4.2 Urine AFM1 sub ppb could be useful for global fighting on stunting<sup>5,7,47,50</sup>:**

Also anthropometric measurement of child overweight/obesity and anamnesis survey.<sup>4</sup> Table 2. said many patients, urine AFM1, p53-p21-p16, mainly of developing countries and low-middle-nSES with senescence,<sup>2,20,21</sup> growth impairment,<sup>1,9,43,46</sup> obese,<sup>11,12</sup> and cancer<sup>1,40</sup> with high urine AFM1 as metabolite of AFB1 in Asia, Africa and Latin America.<sup>4,11</sup>

#### **4.3 Brazilian overweight has also been associated with stunting:**

Geographic wet and warm climate, a good condition for *Aspergillus* sporulation, produce AFB1 exposure, and induce stunting Table 1, by upregulated p16 gene which the p53-p21-p16 axis could be described in Fig. 1. Imported food goes nSES globally.<sup>11</sup> So reported overweight,<sup>12</sup> obese,<sup>11</sup> and Diabetes.<sup>25</sup> A systematic review on the prevalence and factors associated with overweight and obesity in Brazilian children and adolescents is about 20-30%, and it was observed that the socioeconomic factors were associated with the outcome, and are subject to change from the adoption of a healthy lifestyle.<sup>64</sup>

#### **4.4 Mitigation AFB1 on food contamination using gamma-ray to fight stunting, overweight, obesity, and cancer:**

Inactivation of aflatoxin B1 by using the synergistic effect of hydrogen peroxide and gamma-ray, has been reported since 1989.<sup>65</sup> Reducing aflatoxin exposure in agriculture is an issue for the prevention of aflatoxin-related health problems.<sup>40,41</sup>

#### **4.5 Urine AFM1 in pg/ml (sub ppb)<sup>5,7,47,50,51</sup>:**

Anthropology measurements (BMI, WC) and keeping the Refrigerator empty, are good lifestyle to prevention from AFs exposure to various cooking spices, especially small red onions and candlenut which are everyday spices in Indonesian cuisine, and should be stored in open-air ventilation air to prevent from AFs exposure.<sup>4</sup>

#### **4.6 Expression of p16 induces transcriptional downregulation of the RB gene Oncogene.<sup>63</sup>:**

In another way, Viral E6/E7 in HPV, HBV, EBV represent the oncogenic activity parallel with inducing senescence barrier of downregulated p16 gene-activate the RB gene.<sup>17,71,72,73</sup>

Decreased prevalence of stunting and increased obese children, confused as successes the project as given of good nutrition for the undernourished and supplement and probiotic. It was never considered that both stunting and obesity took place successively following in order in sequence obese after stunting, through the senescence barrier (methylation promoter of p16 gene) period. An independent cross-sectional household survey for 12 years, of children from Alagos, Northeast Brazil was reported has the prevalence of stunting and overweight, both were very close in 2005 and if the trends were maintained, at this time, the childhood overweight prevalence has already exceeded that of the stunting.<sup>74</sup>

## **V. LIMITATION**

It is reported that p16(INK4a) in p53-p21-p16 axis, upregulated (growth impairment) than down regulation (proliferation) after the senescence barrier, but many studies do it partly in period of age,<sup>74</sup> associated with nSES.<sup>74</sup> Our study joint both the whole life how p53 mutation, upregulated p21 then p21 downregulated, which upregulated p16 (growth impairment) in stunting and precancerous or good survival stage per individual. By the downregulated p16 genetic or epigenetic hypermethylation, proliferation of cancer cells and migration take place. The aflatoxin exposure could be also intrauterine since pregnancy,<sup>68,69,42,52,70</sup> which the exist of senescence barrier (DNA methylation) reported in infant.<sup>70</sup>

Epidemiology of high prevalence of stunting, obesity, and CKD1 in low- middle-nSES/ income populations in developing and developed countries (AFB1 exposure),<sup>18</sup> Fighting for AFB1 exposure should become a political concept led by the legislative. The molecular pathway based on p53-p21-p16 axis biology molecular signaling in proven sub-ppb technology aspect in nSES population should be known by the people. Till now, it has been considered, an effort to target fighting stunting could be genetic,<sup>75</sup> deficient of zinc<sup>76,77</sup> and another supplement, meta-analysis probiotic,<sup>78</sup> and undernourished dueto gut health.<sup>2,79</sup> Agriculture & Health setting to address this aflatoxin problem, has called us to participate.

## VI. CONCLUSION

Evidence-Based Diagnosis of AFB1 exposure by urine AFM1 sub-ppb marker for public services, could decrease the prevalence of stunting which should be paralleled with Indonesian heritage management from A to Z to get zero-level food free of AFB1 exposure. Various molecular pathophysiological effect was already known as p53-p21-p16 axis pathways, that upregulation of p16INK4a slow down the G1/S cell cycle and support the cause of stunting.

Urine AFM1 level represents aflatoxin B1 exposure is needed for public services simply to convince people, policymakers, legislation is urgent to fight stunting. We propose that legislation should address the role of AFB1 exposure in the pathogenesis of stunting and evaluate interventions to limit AFB1 exposure directly (UPLC) or indirectly (BMI/WC/SsST/refrigerator fullness) to reduce childhood stunting. Stunting and obesity are markers especially vulnerable to mycotoxin exposure.

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## CONFLICT OF INTEREST

The author declares the possession to fight AFB1 exposure with no vested interest in it.

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